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Bubonic plague, a problem of the past, and a re-emerging threat

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Bubonic plaque is caused by *Yersinia pestis*, which is known as fatal diseases in history. The Justinian plaque, Black death, and modern plaque are the three pandemics that have been recorded in the past. Each plaque pandemic caused gigantic mortalities and has become defining situations in the periods in positively affected areas. Natural plaque foci in rodents globally, which is one of the risk factors for human plaque. While bubonic plaque is a sporadic disease in many countries, more than 85% of plaque cases still occur in Africa and other countries. This paper describes the fatalness of Yersinia pestis in the modern world by considering its occurrence and disease severity, transmission, antibiotic resistance, and its potential as a bioweapon. Y. pestis can be used as bioweapons and bioterrorism activities worldwide and has a potential threat to cause millions of deaths in densely populated areas. Training should be done for the awareness of bioterrorism to the general public. Advance research is necessary to search for alternatives to antibiotic cure to fight against the risk of plague. Different management and preventive strategies should be considered, which are less costly and effective against the re-emerging threat of plague to the current world.

Keywords: plague, bubonic, bioweapon, Yersinia pestis, black death

INTRODUCTION

Bubonic plague is a well-known vector-borne infection spread through fleas to many kinds of wildlife rodents, representing natural hosts for this infection in a broad range of habitats throughout the world (Eisen et al. 2007). Alexandre Emile Jean Yersin, a bacteriologist in the Pasteur Institute, discovered *Yersinia pestis* in the Hong Kong (plague outbreak) in 1894, So it was declared by Alexandre that *Yersinia pestis* was the etiological agent of this bubonic plague (Barr et al. 2020). In humankind's history, various

pandemics that have primarily spread from Central Asia to Africa and Europe, and the plague was one of them. In the last 150 years, the plague has spread in every region of the world (Barr et al. 2020). In the 21st century, the plaque has been reported in Asia, Africa, and America, but its recent outbreak was reported in Uganda, Madagascar, Congo, and China. It is noted that the plague is becoming a significant public health issue around the world (Zhao et al. 2016).

Yersinia pestis is a gram-negative, coccobacillus, non-motile, non-spore-forming bacteria, and it presents as bipolar when stained with Giemsa, Wright, or Wayson staining and Gram staining. It persists in various temperatures and pH, such as 28-30 C and pH of 5 to 9.6. *Y. pestis* is very sensitive to UV light, desiccation, and it inhibits their growth spontaneously when the temperature exceeds 40 C. *Y. pestis* emerged from the zoonotic enteric pathogen Yersinia pseudotuberculosis (Prentice & Rahalison, 2007). *Yersinia pestis* is analogous to the Yersinia pseudotuberculosis (enteric pathogen) on the genomic level. However, a chain of gene mutation events has occurred, which leads to the difference in the mechanism of disease, habitat, and appearance (Meyer et al. 2007). *Y. pestis* shows a distinct set of virulence factors that permit the illness of fleas and subversion of immunity in the mammal's reservoir, which led to the sudden death of the host due to the lack of therapy. It takes over the host immune system through bacterial strategies and persists for a long time even after the death of their host. Some of its protein is involved in virulence, including protease Pla and proteins on the outer surface (Yops) (Garmory et al. 2004).

Transmission

Rodents are the main reservoir in Yersinia pestis' life cycle, and this disease is transferred from the hematophagous adult fleas to their hosts, including animals and humans. Infected hosts can become a permanent host for this bacterium. This infection can also be found in other animals like carnivores, lagomorphs, hyracoids, primates, insects, and marsupials. Birds and mammals are killed by plaque hosts and play an essential role in indirectly spreading plaque infection by transferring the infectious fleas among areas (S. Wang et al. 2004). The *Yersinia pestis* become endemic in many regions of the world and are balanced by the animals' population, making them responsible for this microorganism. Plaque infection can be transferred through droplets from one person to another person via coughing. It can also be transmitted through the contaminated fluid of the body. Furthermore, people closely working with animals such as animal husbandry or butchery and farming are at high risk of this infection (Popov et al.2019).

Detection

Several methods can be used for the detection of *Yersinia pesti*s. The fraction 1 (F1) capsular antigen can target the detection of this microorganism because it is responsible for the bacterial immunogenic specific protein (Eroshenko et al. 2020). The passive diagnostic techniques which are used mostly are the hemagglutination inhibition test and hemagglutination test. In the field, the most frequent test used is by the dipstick detection method. The fieldwork areas can be affected during visits where the care testing of *Y. pestis* is conducted to identify pathogens without having access to the laboratory. The medical staff performed polymerase chain reaction (PCR) in the field with real-time quantitative PCR thermocyclers for the detection of the pathogen (Derbise et al. 2020). Several other methods are employed, such as serodiagnosis, upconverting phosphor technology-based biosensor, lateral flow immunoassay, and biosensor to detect the pathogen.

In agreement with the European policy (Decision No 082/2013/EU), the EMERGE Coordination and the Bundeswehr Institute of Microbiology suggest detecting plague by comparing a first positive/negative test result with a second test. For instance, a real positive impact is found by the PCR amplification of a culture or parallel immunological tests. EMERGE also suggests that new laboratory investigations be measured due to obtaining negative results when evaluating an early stage of disease when there is suspected plague and progression of clinical symptoms (Yang et al. 2007).

Treatment

The treatment procedure for the plague should be started as early as possible. The new handling procedure for the plague could be done by utilizing antibiotics, giving out of oxygen, intravenous injections, and respiratory support. The three most essential antibiotics suggested for curing plague are streptomycin, chloramphenicol, and tetracycline. The other antibiotics that can be utilized to cure plagues such as gentamicin, doxycycline, levofloxacin, ciprofloxacin,

moxifloxacin, and chloramphenicol (Kugeler et al. 2015).

Several alternative treatments are listed in the literature: phage therapy, serum therapy, and bacteriocin therapy. Historically, in 1897 Alexander Yersin developed the serum method as a therapy to cure humans by using horse serum (Spyrou et al.2018) However, Serum therapy did stimulate some side effects, such as anaphylactic shock and serum sickness. Regardless of this, a significant difference in mortality rates was established among people suffering from bubonic plague, in which 13% were treated with serum therapy, and 64% for those untreated were reported. At that time, the decline in mortality rates was not significantly diverse among people who suffer from the septicemic or pneumonic plague (Achtman et al. 1999).

In 1925 d'Herelle was first introduced phage therapy using bacteriophages to cure four cases of bubonic plague by isolating active antiplague phage found in rat feces. After injection of phages suspension into the buboes, waited for several hours to observe visible changes in the patient's health; that patient felt healthier and had a 2 °C average fall in temperature and feeling less pain in the buboes. All four patients recovered by this method (Anisimov & Amoako, 2006). However, conflicting results had been seen on animal models while checking the effectiveness of the treatment. This was due to several reasons such as inadequate knowledge of the whole scenario of phage with bacterial interactions, poorly planned and conducting experiments and scientific trials, and the use of not well-defined phages in the shape of non- purified phage arrangements. Regardless of this, phage therapy is getting attention to fight against bacterial antibiotic resistance (Lowell et al. 2007).

In 1970 Bacteriocin McGeachie was introduced bacteriocin therapy in which antimicrobial peptides formed by bacteria were utilized to cure bacterial infections. Purified colicins V and K were showed parallel inhibitory actions as kanamycin, oxytetracycline, and streptomycin. Another bacteriocin called Enterocoliticin was isolated against *Yersinia enterocolitica,* which is closely related to *Y. pestis*. The cure was confirmed to be very efficient in the initial infection (Kortright et al.2019).

Preventive measures

Plague is considered as a quarantinable infectious disease. The first protective measure is to prevent the spread of plague by increasing the surveillance of the illness, particularly at entry points into the countries to ensure that it does not cross other non-infected countries' boundaries. This covers persons, baggage, cargo, containers, conveyances, and goods (Keeling & Gilligan, 2000). The WHO International Health Regulations also suggested that inspection and management of vector supervision should be passed on products that come into the country. Complete monitoring of the rodent populations within a country must be made. For instance, if there is an extreme decline in rat populations, there is a danger of fleas feeding on other animals, which might be the reason for the human epidemic (L, 2003).

Training should be increased for public understanding of the plague (Zhou et al.2020) must be considered (Zhao et al.2016). Emergency planning within all health zones in countries at danger of plague spread must be carried out .In Hong Kong, an administrative region of China, the plague is considered as a notifiable disease. The Department of Health is authorized to manage the plague's spread and the finding source and contact during which the connections will also be specified post-exposure prophylaxis (Ngeleja et al. 2017).

Vaccination is used as a preventive measure to control plague infection. Live attenuated vaccines are consumed in few countries, such as in Russia. The US army introduced killed whole-cell vaccine in the USA. Today vaccines are not destroyed for plague infections due to some challenges reported linked to vaccination for the plague. For example, safety-related challenges have been gaining attention for the use of live attenuated vaccines (Sebbane et al. 2006). For the development of a new type of vaccine for the plague, many kinds of research are made nowadays. Different antigens are used in the development of the subunit vaccine. Simultaneously, the F1 antigen is not best as few strains of *Yersinia pestis* do not make this antigen. The V antigen may be chosen to complement the F1 antigen. There is an option to choose genetically modified vaccines using a strain called Kimberley 53 that formed ten to hundred-fold higher antibody titers to F1 and V might be attenuated and consumed as a live-attenuated vaccine (Zhou et al. 2019).

Furthermore, DNA vaccines might be incorporated by the use of F1 or V antigen DNA. This kind of vaccine is estimated to be valuable as a component of a prime-boost approach. While different types of plague vaccines have been in

the development phase, no verified efficient vaccine for plague control is now available. However, there might be a chance of combining the vaccines with antibiotics for the use of treatment. Researchers have currently reported a combined protective consequence by using a live vaccine after exposure to the bacteria with second-line antibiotic treatment (Shen et al. 2020).

Types of plague

There are mainly three types of plague, and only some are atypical variants of infectious disease. The first and most frequent infection is the bubonic plague. *Yersinia pestis* enters into the lymphatic system after the bite of an infected flea and replicates itself at the lymph node points, resulting in the form of inflammation. The incubation periods of this bacterium is from one to ten days. In the second stage of infection, the bubo can be formed, and open sores might be filled with pus. At this stage, the infection spreads further to the lungs and steps forward into more serious clinical symptoms. The bubonic plague symptoms included chills, fever, malaise, headache, weakness, myalgia, and other few common symptoms are nausea, vomiting, and dizziness (J. Wang et al. 2002). If bubonic plague is not treated on time, the fatality rate between 40 and 70 might be expected. The cases from 80% to 95% due to plague would be expected across the world. When the infection is appropriately treated, the case mortality rate is 5% to 15%.

The pneumonic plague is another type of plague in which lungs are affected very severely and could be an advanced stage of bubonic plague due to infection from a person infected with pneumonic plague. This virulent type of the plague has the fasted beginning with the incubation period as short as one day to 4 days (Mark G. Kuczewski, 2019). The pneumonic plague symptoms are fever, weakness, and headache, a quick-rising in pneumonia with shortness of breath, cough, chest pain, and sometimes the formation of bloody and watery mucous. Pneumonic plague is a more severe infection as compared to bubonic plague. If pneumonic plague is not treated on time, it always resulted in people's death, but those who can survive from the infection should be treated with immediate medication after the appearance of clinical symptoms. The treatment within one day can be unaffected due to less time frame for treatment; therefore, the cases resulting from infection have a high mortality ratio of about 50% (Chen et al. 2010).

The third type of plague-infected blood and known as septicemic plague. Septicemic plague accounts for about 10% to 15% of cases of plague each year. Septicemia may also take place as a secondary infection from bubonic plague. People of all ages can infect by this infection, but the risk for the elderly is more in this type of plague (Perry & Fetherston, 1997). *Yersinia pestis* replicates very rapidly and affects the body by developing a self- perpetuating immunological cascade. This produced an extensive range of fever, chills, weakness, abdominal pain, and shock. The more severe symptoms are disseminated intravascular coagulopathy, acute respiratory distress syndrome, multiple organ failure, hemorrhage in the skin and serosal surfaces, and gangrenous necrosis of acral regions. Septicemic plague is deadly if not treated. With medication, the case mortality ratio ranges from 30% to 50% (Song et al. 2004).

The rare pharyngeal plague is another type of plague. People can get infected by eating raw or undercooked meat from an animal that has been contaminated with *Y. pestis*. Even though the pharyngeal plague has clinical symptoms related to those of other plagues, the pharyngeal plague includes the following symptoms: pharyngitis, tender submandibular lymphadenitis, dysphagia, tonsillar enlargement, and abdominal pain. Pharyngeal plague is mostly found in the Middle East, North Africa, and Central Asia. Gastrointestinal plague is another rare form of plague. The cause of infection is raw or undercooked infected meat. Other diseases linked with the plague recorded are the cutaneous plague, meningitis, and endophthalmitis (Poland & Dennis, 1901).

Distribution of natural plague foci

Plague infection is prevalent in most countries around the world while endemic in a considerable area of the globe. Some states are failed to report the cases of plague due to a lack of sufficient resources. The effect due to plague around the world might be unrepresented in data. Approximately 90% of cases of plaque infection are still reported in South Africa. The Democratic Republic of the Congo, Peru, and Madagascar is the most endemic countries. In each year, most of the plaque outbreaks are reported among the population in Madagascar. On the 5th of March 2019, a recent outbreak was reported at the Uganda-Congo border (Zhou et al. 2020).

In 2017 the outbreak of plague infection

occurred in Madagascar, in which a total of 2,417 confirmed cases were reported. The mortality cases were 209 reported indicating the fatality ratio of 8.6%. In that outbreak, very high numbers of pneumonic plague cases were reported to total 1,854, of which 76.7% ratio was pneumonic plague cases. There bubonic confirmed cases 355 consisting of 14.7% of cases. There is no single case of septicemic plague and 207 cases that have not been identified. This outbreak was different from the other outbreaks occur in Uganda, where 7.1% cases of pneumonic plague were reported, and in the USA, about 8.1% of pneumonic plague cases were reported (Holt et al. 2009).The recommendations made that human to the direct human transmission was found in the 2017 outbreak of Madagascar. The immense cases were found in an unusually small region of the country. Younger patients were most affected by the plague. Madagascar's plague cases among the under 19 age population were reported with the ratio of 60.9% Between the 1996 and 1998 time period. At the same time, 80% of cases were reported among the people up to 29 during the outbreak. In Uganda, 2008 to 2016, the people under the age of 19 were infected with the related pattern, and the majority of cases were recorded in patients (Morelli et al. 2011).

There were 16 plague cases reported in the USA from 2000 to 2012. The country's large area has a reasonable explanation for the low cases of plague in the American public might be fewer possible to come in contact with rodents or other carriers of the plague. Eight veterinarians were affected by this plaque. five people also were affected who worked with animals (e.g., wildlife biologist or animal control personnel), and in the USA, five researchers in the plague laboratory might be affected by these work-related hazards. Pets such as dogs may also make it easy to transfer infected fleas into homes with closeness and contact with their owners (Summers, 2010).

Bioterrorism potential

According to CDC, the *Yersinia pestis* microorganism is placed in Category A organism. Category A organisms are highly pathogenic organisms that need excellent attention to control due to significant risk and can easily be transmitted from one person to another by direct contact and resulting in a high death rate, therefore, poses a health hazard to national security. *Y. pestis* infection needs practical actions for public health awareness (Spyrou et al.2019) Recently, plaques are under control due to natural circumstances and still being a rare disease found in most parts of the world where it is still endemic. *Yersinia pestis* can be used as a bioweapon and may become one of the world's biggest future challenges. The thought of using the plague as a biological weapon is not the latest and has been developed since World War II (Spyrou et al.,2019).

The history of bioweapon began when the Japanese military researchers started their research on *Yersinia pestis* to use as a bioweapon. The plan was monitored by Shiro Ishii (1932–1942) and Kitano Misaji (1942–1945); the research was conducted by a group called Unit 731. The infected rats were used in the laboratory on which fleas were fed to make the first biological weapon for plague infection. The infected wheat and rice with infected fleas were spread over the different Chinese cities to begin a plague epidemic. One case was reported in Ningpo, where 100 people death cases were recorded due to plague after the attack of fleas onto the city. While these attacks were conducted successfully, this did not have a good deal of an outcome on the war (Spyrou et al. 2018).

After World War II, successful trials were made on *Yersinia pestis* to use as bioweapons in the Soviet Union and the USA. These two countries designed a different technique for introducing *Y. pestis directly* by aerosolizing the plague without using fleas as carriers. This work enables scientists to make different types of plaque to infect humans with bioweapon's unpredictable specialty (Death et al. 2012). The spread of Y. pestis increased the bubonic plague cases via fleas. The pneumonic plague is more severe and virulent and spread by aerosol. In 1970 the WHO recommended that in the worst-case circumstances, that if 50 kg of *Y. pestis* was spread in a city with a resident of 5 million, up to 150,000 individuals might be infected, and 36,000 of the population would be predictable to die (Morelli et al. 2010).

Today, most countries have closed conducting offensive bioweapons researches. In the 1950s, the United Kingdom ceased to follow by the USA. The Biological and Toxin Weapons Convention was informed in 1969 and more forward the British's summary and finished by the Soviet Union even though the final did not separate their bioweapons program until 1992. The research was conducted on Yersinia pestis strain by the Soviet Union, indicating that the genetically modified bacteria have multidrug-resistant and fluoroquinolone- resistant. In the

incidence that this bioweapon was to be spread, the antibiotics that would have been consumed are streptomycin, tetracycline, fluoroquinolones with doxycycline, gentamicin, ciprofloxacin or chloramphenicol used as alternatives treatment against pneumonic plague. This would have also involved giving antibiotic prophylaxis with doxycycline or ciprofloxacin for one week to everyone who comes into direct contact with the pneumonic plague (Achtman et al. 1999).

In a biological threat, affected countries would need planned biosafety administration the surveillance, subsequent investigation, cure, and control of plague infection. *Yersinia pestis* can be used as a bioterrorism danger due to various factors that formulate for this use. The first approach is the accessibility of *Y. pestis* in those countries where it is endemic and then searched the possibility of isolated and cultured the bacteria in a laboratory. Furthermore, information about the growth condition and the optimum environment is available. Secondly, infection is caused by Y. pestis has a high death rate while in pneumonic plague infection, the transmission of disease spread quickly among the people. Thirdly, to access the previous research left behind by senior researchers who researched *Y. pestis* could be exploited with the objective of bioweapons strains. The challenges related to antibiotic resistance against *Y. pestis* strains could be affected by many countries to control the infection and deal with the delivery of cure (Kugeler et al. 2015).

Antibiotic resistance

Bacterial antibiotic resistance against bacterial infections is now a global challenge. The dilemma of antibiotic resistance falls in the bacteria's capability to transport its antibiotic resistance gene plasmids using the conjugation process to further non-resistant strains of *Y. pestis* or to *E. coli*. In previous research, the isolated strains in Madagascar showed antimicrobial susceptibility against antibiotics. Currently, two strains of *Yersinia pestis* were showed resistance against antibiotics. *Y. pestis* 17/95 carries eight antibiotic resistances on a plasmid of 150 kb called pIP1202 and is reported to exhibit high-level resistance to eight antimicrobial agents used for treatment and some prophylactic drugs. Emerging of antibiotic resistance towards bacterial strains is nowadays the most important global issue. Recently, bacteria are showing numerous transformations in their genetic makeup and developing resistance genes against different antibiotics; these resistance plasmids via conjugation may be transported to non-resistant strains of *Y. pestis* and *E.coli* (Anisimov & Amoako, 2006).

The resistant genes are also shown resistance against several classic alternative drugs such as ampicillin, spectinomycin, and kanamycin. *Y. pestis* 16/95 has just resistance against streptomycin on a plasmid of 40 kb known as pIP1203. It remains vulnerable to further antibiotic treatments. The transfer of plasmid genes is responsible for antibiotic resistance to *E. coli* because *E. coli* has a recognized history of bacterial strains transmission of antibiotic resistance. Recently, both of these strains are linked to Madagascar. The other countries in which the plaque is endemic, so there could be many chances of spreading resistant genes among the plaque population. It could also spread among other bacteria in the same manner that it does with *E. coli.* Furthermore, if few *E. coli* bacteria have the plasmid genes, which are resistance genes responsible for resistance, they might be transferred to other bacteria (Poland & Dennis, 1901).

The increasing level of antibiotic resistance in Madagascar may direct governmental authorities to start research studies to find alternative methods against antibiotic treatments. For instance, alternative medicine approaches through bacteriophage therapy are ultimately estimated to become one of the most successful antimicrobial alternatives. The bacteriophage therapy is more efficient than serum therapy, while bacteriocin therapy as the bacteriophages merely kills the targeted bacteria. Another advantage of the bacteriophage is that phage mutation is significantly higher than bacterial transformation, so it responds quickly to phage-resistant bacteria mutants. Bacteriophages are also cheaper to develop than new antibiotics. Besides, few sides- effects from bacteriophage treatment have been reported. Nevertheless, bacteriophage treatment development may face some challenges such as toxin encoding amongst phages, a lack of pharmacokinetic data, and neutralization of the phase by the host immune system leading to the failure of the treatment (Demeure et al. 2019).

Trade routes, human travel, and economic consequences

Today the trading is made through the air and sea routes to the other parts of the world. The ancient trading routes provide supports to spread the *Y. pestis* at a high rate from Madagascar to

around the globe. The trading of wildlife can become a potential source to transport zoonotic diseases to other countries. Madagascar has a considerable number of exports that go across the world. The major export is vanilla, which is transported to several other countries among top importers such as China, France, the USA, Japan, and Germany. Therefore, there are many chances for *Y. pestis* to be transported among these trade ways to other countries (Morelli et al. 2010). The spread of *Y. pestis* among the tourist who reached Madagascar from around the world for tourism has *a* high potential to cause disease during the season when the plaque is much prevalent. Tourists may get infected and return to their home countries before symptoms appear. In 2017 during the outbreak in Madagascar, overseas territories, including nine countries, were marked as major concern countries for plague attentiveness due to travel and trade connection to other countries from Madagascar. These countries, including overseas territories, were South Africa, Comoros, Seychelles, Ethiopia, Kenya, Mozambique, La Réunion (France), Mauritius, and Tanzania (Cao et al. 1995).

The consequence of plague is harmful in countries throughout and after outbreaks. The cost of affected locations worsens local business markets and loss of profits to the public areas that had to be closed. For example, in 1994, the outbreak in Western India affected food markets, restaurants, and public places. This plague was comparatively minute, with 700 report cases of plague. However, due to the panic of the spread of plague infection, numerous restrictions were imposed upon the sea and air voyage and India's trade consequent orders from health authorities. This caused the fall of business and the tourism sectors, which caused the expected 1.8 billion US dollars to harm the economy. The outcome of this was a crash on public life and India's financial system at that moment (White & Mordechai, 2020).

CONCLUSION

This article gives information about the risk of *Yersinia pestis* in the current world. The plague can cause numerous fatalities across the globe if it is not restricted or be used as a bio-weapon. The taxonomy of plague reflects a re-emerging disease that may cause a high figure of cases in entire Madagascar, indicating that Y. pestis can develop life-threatening situations to a country if not controlled correctly if the environmental factors are favorable for it. The emergence of antibiotic resistance becomes a problem against two strains of *Y. pestis* may become a life-threatening problem in the future if alternative antibiotics or other treatments are not discovered. *Y. pestis* can be used as bioweapons and bioterrorism activities worldwide and has a potential threat to cause millions of deaths in densely populated areas. Training should be done for the awareness of bioterrorism to the general public. Advance research is necessary to search for alternatives to antibiotic cure to fight against the risk of plague. Different management and preventive strategies should be considered, which are less costly and effective against the re-emerging threat of plague to the current world.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

NZ designed the idea and also wrote the manuscript. AA and MAA reviewed the manuscript. All authors read and approved the final version.

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