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***Yersinia pestis*, a problem of the past and a re-emerging threat**

REVIEW ARTICLE

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ABSTRACT

Yersinia pestis is the bacteria that causes plague, one of the deadliest diseases in human history. Three major plague pandemics (The Justinian Plague, the Black Death and the Modern Plague) have been recorded. Each caused massive fatalities and has become defining events in the time periods in places that were affected. The presence of natural plague foci in rodents across the world is one of the risk factors for human plague. While plague is a relatively rare problem for most countries, more than 90% of plague cases in the world still occur in Africa. This article discusses the threat of *Yersinia pestis* in the modern world by considering its prevalence and severity of illness it causes, transmission, antibiotic resistance, and its potential as a bioweapon.

Keywords: *humans, plague, Yersinia pestis, bioterrorism, pandemics, drug resistance, microbial, Africa*

1. Introduction

Plague is an infectious disease caused by *Yersinia pestis*, a gram-negative, nonmotile, non-spore-forming coccobacillus. This bacteria appears as bipolar staining with Giemsa, Wright's, or Wayson staining and is also visible by Gram staining. It survives within a wide range of temperatures with the optimum being 28°C to 30°C with pH extremes of 5 and 9.6. *Y. pestis* dies very rapidly if exposed to a UV light, temperatures exceeding 40°C or when exposed to intensive desiccation [1].

Yersinia pestis evolved from the closely related zoonotic enterobacterium *Y. pseudotuberculosis* [2]. *Yersinia pestis* strain CO92 was amongst the first bacteria to be sequenced [3]. Other strains have since been sequenced [4–6,6–8]. The fluid nature of its genome and molecular mechanisms contribute to its resilience, virulence and ability to persist even after the death of its host [3]. For instance, the bacteria evolved to acquire plasmids which enables it to transition into its rodent-flea environments and enhance virulence [9]. The bacteria also has specific genes involved in host virulence, host colonisation and core cellular function [10]. *Yersinia pestis* uses bacterial strategies to take over host innate immune responses and prolong its own survival. Its virulence is determined by specific proteins such as the protease Pla and the *Yersinia* outermembrane proteins (Yops) [11].

Y. pestis has three different biovars in which each causes a distinct pandemic. The three distinct biovars are Antiqua, Medievalis and Orientalis. Antiqua is found in Africa and central Asia whereas Medievalis is limited only to central Asia and Orientalis is almost worldwide in its distribution [12]. Recently, researchers reported a new biovar called Microtus, found in China [13]. The differences between the biovars can be seen on the basis of conversion of nitrate to nitrite and fermentation of glycerol. The first

1 strain Antiqua has both characteristics. Orientalis converts nitrates to nitrites but does
2 not ferment glycerol. Medievalis does not possess either of the characteristics to
3 convert nitrates to nitrites or fermenting glycerol [10]. The Microtus strain shows similar
4 characteristics with those of Mediavalis and does not utilise arabinose [13].
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6 1.1 Transmission

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8 The life cycle of *Yersinia pestis* involves rodents and its transmission from
9 hematophagous adult fleas to animal hosts and between hosts, including humans.
10 Infected animals and their fleas can become long-term reservoir hosts for the bacteria.
11 Infections can also occur in other animals such as lagomorphs, artiodactyls,
12 carnivores, hyracoids, insects, marsupials and primates. Birds also have the tendency
13 to spread fleas that carry *Y. pestis* while predators catch prey that may carry the
14 bacteria, which in turn spreads the bacteria around. Thus, *Yersinia pestis* is
15 maintained in nature by animal populations making them accountable for this bacteria
16 being endemic in many parts of the world [14]. Plague infection can occur from person
17 to person through infectious droplets from the coughs of infected people and contact
18 with contaminated bodily fluid or tissue [15]. Besides bites from infected fleas, people
19 working with animals such as farming, butchery or animal husbandry are at risk of
20 plague infection [16].
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25 1.2 Detection

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27 There are a number of ways in which *Yersinia pestis* can be detected. Most target the
28 fraction 1 (F1) capsular antigen which represents the most immunogenic specific
29 protein of the bacteria [17,18]. The most widely used diagnostic tests are the passive
30 hemagglutination test and hemagglutination inhibition test. Dipsticks are the most
31 frequently used detection methods in the field [19]. Point of care testing of *Y. pestis*
32 during field work or visits to affected areas allows detection in the field without having
33 to access a laboratory [20]. Detection by Polymerase Chain Reaction (PCR) may be
34 performed by medical staff in the field by using portable real-time quantitative PCR
35 thermocyclers [15]. Other detection methods such as biosensors [21,22],
36 serodiagnosis [23], lateral-flow immunoassay and up-converting phosphor
37 technology-based biosensors [24] have since been introduced and successfully
38 evaluated.
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44 In compliance with the European policy (Decision no 082/2013/EU), the EMERGE
45 Coordination and the Bundeswehr Institute of Microbiology recommend detecting
46 plague by confirming a first positive/negative test result with a second test. As an
47 example, a positive PCR amplification confirmed by a culture or immunological test
48 conducted in parallel. EMERGE also recommends that additional laboratory
49 investigations be considered in the event of obtaining negative results when evaluating
50 an early stage of disease when there is suspected plague and progression of clinical
51 symptoms [25].
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54 1.3 Treatment

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56 Treatment for plague should administered as soon as possible [26]. The current
57 treatment for plague includes the use of antibiotics, dispense of oxygen, intravenous
58 fluids and respiratory support [27]. Three main antibiotics recommended to treat
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1 plague are streptomycin, tetracycline and chloramphenicol [27]. Other antibiotics that
2 can be used to treat plague are as gentamicin, levofloxacin, ciprofloxacin, doxycycline,
3 moxifloxacin and chloramphenicol [28].

4
5 Alternative methods of treatment in the literature comprise serum therapy, phage
6 therapy and bacteriocin therapy. Historically, serum therapy to treat humans with a
7 horse serum was conducted by Alexandre Yersin in 1897 [29]. Serum therapy
8 however, did induce side effects such as serum sickness and anaphylactic shock.
9 Despite this, a significant difference in death rates was found amongst people suffering
10 bubonic plague, for which 13% was reported for those treated with serum therapy and
11 64% for those untreated. At that time, reduction in death rates was not much different
12 between people suffering from septicaemic or pneumonic plague [26,30].
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16 Phage therapy through bacteriophages was first attempted by d'Herelle in 1925 to
17 treat four cases of bubonic plague by using highly virulent anti-plague phage that had
18 been isolated in rat faeces. Within several hours after the injection into the buboes the
19 patients began to feel better and had 2°C average fall in temperature and decreased
20 pain in the buboes. All four patients made a recovery. However, when trying to confirm
21 the efficacy of the treatment using animal models led to conflicting results. This was
22 due to a number of factors such as a poor understanding of the mechanisms of phage–
23 bacterial interactions, poorly designed and executed experiments and clinical trials
24 and the use of undefined phages in the form of non-purified phage preparations [31].
25 Despite this, phage therapy is gaining renewed interest to combat antibiotic resistant
26 bacteria [32].
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31 Bacteriocin therapy through bacteriocins, antimicrobial peptides produced by bacteria
32 was used by McGeachie in 1970 to treat bacterial infections. Purified colicins V and K
33 were found to show similar inhibitory activities as kanamycin, streptomycin and
34 oxytetracycline [33]. Another bacteriocin called Enterocolitacin was tested against
35 *Yersinia enterocolitica* which is a close relative of *Y. pestis*. The treatment was proven
36 to be effective in the early phase of infection [34].
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40 *1.4 Preventive measures*

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42 Plague is classified as a quarantinable disease. The first preventive measure is to stop
43 the spread of plague by enhancing surveillance for the disease especially at points of
44 entry into countries to ensure that it does not cross borders into other non-infected
45 countries. This covers persons, baggage, cargo, containers, conveyances goods [35].
46 The WHO International Health Regulations also recommend that inspection and
47 supervision of vector surveillance should be carried out on products that enter the
48 country. Monitoring of the rodent populations within a country should be conducted.
49 For example, if there is a drastic decrease in rat populations, there is a risk of fleas
50 feeding on other animals which may bring upon a human epidemic [36].
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55 Measures to increase public awareness of plague[37] should be undertaken [35].
56 Contingency planning within all health sector partners in countries at risk of plague
57 spread should be carried out [38] In some countries such as Hong Kong, plague is a
58 statutory notifiable disease. As such, the Department of Health is authorised to control
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1 the spread of the plague including source finding and contact tracing during which the
2 contacts will also be given post-exposure prophylaxis [35].

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4 Vaccination is a preventive measure for the plague [39–41]. Live attenuated vaccines
5 are used in some countries such as Russia [15]. There is also the killed whole cell
6 vaccine in use produced by the US army [42]. Due to many reported challenges related
7 to vaccination for plague, vaccines are not common in use today. For instance, safety
8 concerns have been raised in the use of live attenuated vaccines [43,44]. Research
9 on new types of vaccines for the plague is vast. Some of those in development include
10 subunit vaccines which use different antigens. Whilst the F1 antigen is not ideal
11 because some *Yersinia pestis* strains do not produce this antigen, the V antigen may
12 be selected to compliment the F1 antigen [42]. There is a possibility that genetically
13 modified vaccines using a strain called Kimberley 53 that produces ten to hundred-
14 fold higher antibody titres to F1 and V could attenuated and used as a live-attenuated
15 vaccine [45]. Furthermore, DNA vaccines could incorporate the use F1 or V antigen
16 DNA [46,47]. This type of vaccine is expected to be useful as part of a prime-boost
17 strategy [45]. While different types of plague vaccines have been in development, no
18 proven effective vaccine for plague prevention is currently available [15]. There is
19 however, a possibility of combining the use of vaccines with antibiotic treatment.
20 Recently, researchers have reported a synergistic protective effect in using a live
21 vaccine upon exposure to the virus with second-line antibiotic treatment [48].
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26 **2. Types of plague**

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29 There are three main types of plague and a few rare variants of the disease. The first
30 and most common is the bubonic plague. After a bite by an infected flea, *Yersinia*
31 *pestis* enters the lymphatic system and replicates itself at the nearest lymph node,
32 causing it to swell and become inflamed. The bacteria then incubates between one to
33 ten days [49]. During the later stages of infection, the bubo can develop open sores
34 filled with pus [50]. At this stage, infection may also spread to the lungs and progress
35 into more severe clinical symptoms. The symptoms linked with bubonic plague are
36 fever, headache, chills, weakness, malaise, myalgia other less common symptoms
37 are dizziness, nausea and vomiting [49]. If bubonic plague is left untreated, the fatality
38 rate is between 40% to 70% fatality rate. This accounts for 80% to 95% of cases of
39 plague worldwide. When treated, the case fatality rate is 5% to 15% [49].
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44 The next type of plague is pneumonic plague where the lungs are infected and can be
45 a progression of bubonic plague to this stage or a progression by an infection from an
46 individual affected with pneumonic plague. This is the most virulent form of the plague
47 and can have the quickest onset with the incubation time sometimes being as short
48 as 24 hours or up to 4 days. The symptoms of pneumonic plague are fever, headache,
49 weakness, and a rapidly developing pneumonia with shortness of breath, chest pain,
50 cough, and sometimes presents with bloody or watery mucous [28]. Pneumonic
51 plague is a more severe infection compared to bubonic plague. If pneumonic plague
52 is left untreated, it is almost always fatal but most people can survive the infection with
53 immediate treatment upon clinical manifestation of the symptoms. Due to the short
54 time frame to obtain effective treatment within 24 hours, the case fatality ratio is greater
55 than 50% [49].
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1 The third type of plague is septicaemic plague where blood is infected. Primary
2 septicaemic plague makes up about 10% to 15% of all cases of plague [51].
3 Septicaemia may also arise as a secondary effect from bubonic plague. It can affect
4 people of all ages, but the elderly are more at risk of developing this type of plague
5 [52]. It affects the body by causing a self-perpetuating immunological cascade due the
6 rapidly replication of *Yersinia pestis* [28]. This causes a wide array of symptoms such
7 as the minor ones like fever, chills, extreme weakness, abdominal pain and shock
8 followed by more severe symptoms such as disseminated intravascular coagulopathy,
9 multiple organ failure, acute respiratory distress syndrome, haemorrhage in skin and
10 serosal surfaces and gangrenous necrosis of acral regions [51]. Septicaemic plague
11 is fatal if left untreated. With treatment, the case fatality ratio lies within the range of
12 30% to 50% [53].
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16 Another type of plague is the rare pharyngeal plague [54]. People who eat
17 undercooked or raw meat from an animal that has been infected with *Y. pestis* can get
18 infected [55]. Although pharyngeal plague clinical symptoms are similar to those of
19 other plagues, those unique to pharyngeal plague are pharyngitis, dysphagia, tender
20 submandibular lymphadenitis, tonsillar enlargement and occasional abdominal pain
21 [56]. Pharyngeal plague is more likely to occur in Middle East [57,58], North Africa
22 [59,60] and Central Asia [61]. Another rare form of plague is gastrointestinal plague
23 [53]. The source of infection is raw or undercooked contaminated meat. Other
24 infections associated with plague which have been reported are cutaneous plague,
25 meningitis, and endophthalmitis [15].
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29 **3. Prevalence and Severity**

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31 Natural plague is prevalent in many countries across the world and is endemic in a
32 large area of the world [62]. In fact, the effect of plague across the world may be
33 underrepresented in data due to unrecognized cases and the failure of countries to
34 report plague cases. While plague is still a relatively rare problem for most countries,
35 more than 90% of plague cases in the world occur in Africa [12]. The three most
36 endemic countries in the world are the Democratic Republic of the Congo,
37 Madagascar, and Peru [50]. Madagascar is the most affected country in the modern
38 world with reports of plague outbreaks in the population every year [63]. In fact, the
39 most recent outbreak at the Uganda-Congo border was reported on the 5th of March
40 2019 [64].
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45 A total of 2,417 confirmed cases were reported in the 2017 plague outbreak in
46 Madagascar [38,65]. The death toll was 209 leading to a case fatality ratio of 8.6%
47 [66]. What stands out about this outbreak is the high amount of pneumonic plague
48 cases totalling 1854, of which 76.7% were pneumonic plague. There were 355
49 confirmed cases of bubonic plague, comprising 14.7% of cases. There was also a
50 single case of septicaemic plague and 207 cases that have not been classified. This
51 outbreak differed to outbreaks that occurred in Uganda where 7.1% cases of plague
52 were pneumonic [67] and the USA where 8.1% of plague cases were also pneumonic
53 [16]. This suggests that human to human transmission was prevalent in the 2017
54 Madagascar outbreak. The majority of cases occurred in a very small area of the
55 country. Younger patients were more likely to suffer from plague [68]. Between 1996
56 and 1998, 60.9% of plague cases in Madagascar occurred in people under the age of
57 19. When affected individuals up to the ages of 29 were included, the number of cases
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1 totalled 80% of all cases during this time [66]. In Uganda, a similar pattern in age
2 groups was found with the most cases reported in patients under the age of 19 from
3 2008 to 2016 [67].

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5 From 2000 to 2012, there were sixteen reported cases of plague in the USA [65]. In
6 view of the vast size of the country, a plausible explanation for the low number of
7 plague cases is that the American public may be less likely to come into direct contact
8 rodents or other carriers of the plague as the public in Madagascar [16]. Plague cases
9 that affected eight veterinarians, five people who worked with animals (e.g. wildlife
10 biologist or animal control personnel) and five plague laboratory researchers in the
11 USA may be attributed to occupational hazards [16,69,70]. Pets such as dogs may
12 also facilitate the transfer of infected fleas into homes through close living proximity
13 and interaction with their owners [71].
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16 **4. Bioterrorism potential**

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19 *Yersinia pestis* is regarded as a Category A organism by the CDC. Category A
20 organisms are considered to be a high priority agent that poses a risk to national
21 security due to its easy transfer from person to person where infection can result in a
22 high mortality rate and public panic. *Y. pestis* infection also requires special action for
23 public health preparedness [28]. Currently, under natural conditions the plague is fairly
24 well controlled with it still being a rare disease to occur even in most areas of the world
25 in which it is endemic. Nevertheless, one of the biggest future dangers may be the
26 imminent threat of plague used as a biological weapon [72]. The idea of using plague
27 as a biological weapon is not new and has been considered since World War Two.
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32 The history of the research and possible use of *Yersinia pestis* as a bioweapon began
33 with the Japanese military's research on the use of many different biological weapons.
34 The program was led by Shiro Ishii (1932–1942) and Kitano Misaji (1942–1945) and
35 the research was performed by a group known as Unit 731 [73]. The first plague
36 biological weapon was made by allowing laboratory fleas to feed on infected rats.
37 Wheat and rice with infected fleas were scattered over Chinese cities to attempt to
38 start a plague epidemic [74]. One case occurred in Ningpo where 100 people died of
39 plague after the release of fleas onto the city. Although these attacks were carried out
40 to relative success, this did not have much of an effect on the war [75].
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45 After World War Two, *Yersinia pestis* continued to be developed in this role, reportedly
46 in the Soviet Union and the USA [76,77]. The two countries developed a method for
47 introducing *Y. pestis* by aerosolising the plague directly without having to use fleas as
48 carriers [78]. This would make the plague an unpredictable bioweapon and could also
49 enable scientists to determine the type of plague to infect victims with. Whilst the
50 release of *Y. pestis* using fleas caused cases of bubonic plague, the aerosol version
51 would cause pneumonic plague which is more virulent and severe [79,80]. In 1970 the
52 WHO estimated that in the worst-case scenario that if 50kg of *Y. pestis* was released
53 in a city with a population of 5 million, up to 150,000 people could be infected and
54 36,000 of those people would be expected to die.
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58 Today, most countries have stopped conducting offensive bioweapons programmes.
59 The United Kingdom ceased in the 1950s, followed by the USA in 1969. The Biological
60 and Toxin Weapons Convention was written in 1969 and further drafted by the British
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1 and completed by the Soviet Union although the latter did not disband their
2 bioweapons programme until 1992 [80]. The *Yersinia pestis* strain that the Soviet
3 Union was working on was genetically modified to be multidrug-resistant and
4 fluoroquinolone-resistant [51]. In the event that this bioweapon were to be released,
5 the drugs that would have been used are streptomycin, gentamicin, tetracycline, or
6 fluoroquinolones with doxycycline, ciprofloxacin or chloramphenicol as alternatives to
7 treat the pneumonic plague outbreak [81]. This would have also included giving
8 antibiotic prophylaxis with doxycycline or ciprofloxacin for seven days to anyone who
9 comes into contact with the patients with pneumonic plague [82].
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11 In the event that a biological threat occurs, affected countries would require strategic
12 biosafety management the surveillance, subsequent investigation, treatment and
13 control of infection [83,84]. *Yersinia pestis* is a bioterrorism threat due to a number of
14 factors that make it fit for this purpose [85]. The first is the accessibility of *Y. pestis* due
15 to the amount of countries it is endemic in and the possibility for it to be isolated and
16 cultured in a laboratory. Furthermore, information for its optimum growth conditions
17 are available [86]. Secondly, infection by *Y. pestis* has a high mortality rate in
18 pneumonic plague which can be easily spread between people. Thirdly, access to
19 previous research left behind by former scientists who worked on *Y. pestis* could be
20 exploited with the intent of weaponising the strain [87]. Last but not least, antibiotic
21 resistance in *Y. pestis* strains [88,89] could pose to be challenging for affected
22 countries to control disease and manage the delivery of treatment and healthcare
23 [36,90].
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30 **5. Antibiotic resistance**

31 Bacterial resistance to antibiotics is a global challenge [81,91,92]. The problem of
32 antibiotic resistance lies in the ability of the bacteria to transfer its antibiotic resistance
33 plasmids via conjugation to other non-resistant strains of *Y. pestis* or to *Escherichia*
34 *coli* (*E. coli*) [93]. Antimicrobial susceptibility of isolated strains in Madagascar have
35 previously been researched [94]. Recently, two strains of *Yersinia pestis* were found
36 to exhibit antibiotic resistance. *Y. pestis* 17/95 carries 8 antibiotic resistances on a
37 plasmid of 150kb called pIP1202 and is reported to exhibit high-level resistance to
38 eight antimicrobial agents used for treatment and some prophylactic drugs. It is also
39 resistant to some of the typical alternative drugs such as ampicillin, kanamycin, and
40 spectinomycin. While *Y. pestis* 16/95 has only streptomycin resistance on a plasmid
41 of 40 kb called pIP1203, it remains susceptible to other antibiotic treatment [81]. The
42 transfer of the antibiotic resistances to *E. coli* may be important as *E. coli* has a
43 documented history of interbacterial species transmission of antibiotic resistances
44 [95]. Currently, both of these strains are confined to Madagascar. If they reach another
45 country in which the plague is endemic, antibiotic resistant genes could be spread to
46 the endemic plague population. It may also spread to other bacteria in the same way
47 that it does with *E. coli* [96]. Furthermore, if some *E. coli* carry the plasmid containing
48 the resistance genes from *Y. pestis*, antibiotic resistance may be transferred to other
49 bacteria [93].
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57 The rising level of antibiotic resistance in Madagascar may lead to governmental
58 pressure to conduct research into alternative methods of treatment instead of sole
59 reliance on antibiotic treatments. An example of alternative treatment is via
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1 bacteriophage[97] which is expected to eventually become one of the most effective
2 antibacterial alternatives [98,99]. The bacteriophage method is offers more specific
3 than serum therapy and bacteriocin treatment as the bacteriophages only destroy the
4 targeted pathogenic bacteria [100]. Another advantage of the bacteriophage is that
5 phage mutation is significantly higher than that of bacteria mutation so it responds
6 quickly to phage-resistant bacterial mutants. Bacteriophages are also cheaper to
7 develop than new antibiotic development. In addition, few side-effects from
8 bacteriophage treatment have been reported [100]. Nevertheless, the development of
9 bacteriophage treatment may face some challenges such as toxin encoding amongst
10 phages, a lack of pharmacokinetic data and neutralisation of the phase by the host
11 immune system leading to the failure of the treatment [100].
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14 **6. Trade routes and human travel**

16 The routes that support the spread of *Y. pestis* strains from Madagascar to other parts
17 of the world are similar to those of historical trade routes. Today, these trade routes
18 via air and sea are as vast as ever. Wildlife trade can potentially bring zoonotic
19 diseases to different countries [101]. Madagascar has a large amount of exports that
20 go around the world. The main export is vanilla which goes to many different countries
21 with top importers such as France, the USA, Germany, China and Japan [102].
22 Therefore, it is possible for *Y. pestis* to be moved across these trade routes to other
23 countries. The spread of *Y. pestis* can happen through human travel via tourism if
24 people travel to Madagascar during the seasons of the year when plague is most
25 prevalent. Tourists may get infected and return to their own country before symptoms
26 appear. During the 2017 outbreak in Madagascar, nine countries and overseas
27 territories were listed as priority countries for plague preparedness due to the trade
28 and travel links of the countries to Madagascar. These countries and overseas
29 territories were Comoros, Ethiopia, Kenya, Mauritius, Mozambique, La Réunion
30 (France), Seychelles, South Africa, and Tanzania [38].
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36 **7. Economic consequences**

37 The effect of plague is detrimental in countries during and after outbreaks. The
38 consequences of affected locations are deteriorating local businesses and loss of
39 income to the public places that had to be shut down. For instance, the outbreak in
40 Western India in 1994 affected food vendors, restaurants, and public gatherings [103].
41 This plague was a relatively small with 700 cases of plague. However, due to the fear
42 of plague infection, many restrictions were placed upon air and sea travel and trade of
43 India following recommendations from health authorities. This caused the collapse of
44 trade and the tourism industry which caused an estimated 1.8 billion dollars damage
45 to the economy. The consequence of this was a definite impact on public life and the
46 economy of India at that time [103,104].
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52 **8. Concluding remarks**

53 This article discussed the threat of *Yersinia pestis* in the modern world. The plague
54 has the potential to cause many fatalities across a global scale if it is not controlled or
55 used as a weapon. The classification of plague as a re-emerging disease with the high
56 number of cases across Madagascar suggests that *Y. pestis* can cause serious
57 problems to a country if left unchecked or if the environmental conditions are suitable
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1 for it [1]. The threat of antibiotic resistance in the emergence of the two resistant
2 natural stains of *Y. pestis* may become a real problem in the future if other antibiotics
3 or alternative treatments are not discovered [81]. The threat of bioterrorism and
4 bioweapons by way of *Y. pestis* has the potential to cause thousands of deaths in a
5 heavily populated area [80,87]. Exercises in bioterrorism awareness and
6 preparedness should be made available to the general public [105]. Further research
7 is needed to find alternatives to antibiotic treatment to combat the risk of plague. Cost-
8 effective and sustainable preventive and management strategies should be deployed
9 against plague, a re-emerging threat to the modern world.
10

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