




Review

# Plague Prevention and Therapy: Perspectives on Current and Future Strategies

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**Abstract:** Plague, caused by the bacterial pathogen *Yersinia pestis*, is a vector-borne disease that has caused millions of human deaths over several centuries. Presently, human plague infections continue throughout the world. Transmission from one host to another relies mainly on infected flea bites, which can cause enlarged lymph nodes called buboes, followed by septicemic dissemination of the pathogen. Additionally, droplet inhalation after close contact with infected mammals can result in primary pneumonic plague. Here, we review research advances in the areas of vaccines and therapeutics for plague in context of *Y. pestis* virulence factors and disease pathogenesis. Plague continues to be both a public health threat and a biodefense concern and we highlight research that is important for infection mitigation and disease treatment.

**Keywords:** *Yersinia pestis*; plague; antibiotic; vaccine; antibodies



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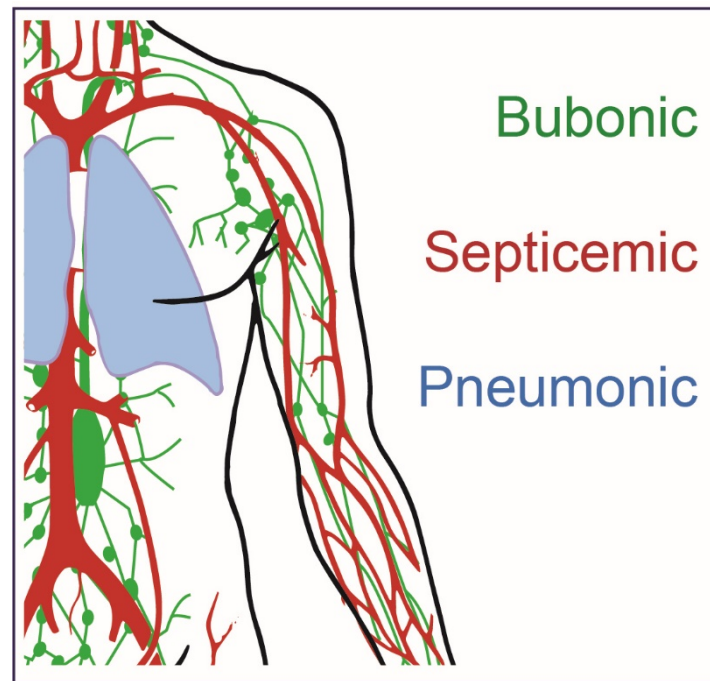
## 1. Plague History and Disease Presentation

*Yersinia pestis* is a Gram-negative coccobacillus that is the etiologic agent of plague, an acute infectious disease that has played an important role in human history [1–5]. This bacterium has been responsible for three devastating pandemics that led to millions of deaths [6–8]. The first pandemic, referred to as the “Justinian Plague”, occurred in 541 AD, originated in Central Africa, and spread to the Mediterranean region [7]. The “Black Death” of 1347 was the second major pandemic and occurred during the 14th century, originating in Central Asia and eventually reaching the Middle East, North Africa, and Europe. The third pandemic took place in 1855 in Yunnan, China and spread globally via infected rats on ships likely originating from Hong Kong [7,9,10]. This bacterium has impacted human civilization throughout history and continues to be of concern [5].

Dissemination of *Y. pestis* among wild rodents and humans takes place in two different cycles, enzootic and epizootic [11]. Enzootic refers to when the infection, at low levels, cycles naturally among wild rodents (e.g., rats, squirrels, marmots, and prairie dogs). Sporadically, other susceptible species can be infected, causing an outbreak—this is referred to as epizootic plague. In this disease cycle, animals become infected and ultimately die as fleas from infected natural reservoir species begin to seek other blood sources and the probability of human transmission is increased [11].

*Y. pestis* can cause three forms of plague disease: bubonic, septicemic, and pneumonic (Figure 1). Historically, the bubonic form of plague has been the most common and can be transmitted to humans by a bite from an infected flea or by handling an animal infected with *Y. pestis* [12–15]. After transmission, the *Y. pestis* bacteria disseminate to the nearest lymph node where they colonize and subsequently proliferate. The incubation time ranges from approximately 2–8 days and during that period patients will experience flu-like symptoms, such as chills, fever and headaches [16–19]. As the bacteria continue to multiply, the lymph nodes become swollen and extremely painful. Infected lymph nodes (referred to as buboes when attributable to plague) are generally found in specific areas of the body, such as

the neck, under the chin, armpits and groin. If left untreated, these buboes can become necrotic and cause hemorrhaging ultimately leading to lethal disease in approximately 50–60% of cases [20]. A culture isolated from a blood sample or fluid from the swollen lymph node may be necessary for the diagnosis and identification of *Y. pestis* [17]. Several classes of antibiotics are effective in treating bubonic plague and if treatment is initiated promptly, antibiotics can significantly increase survival rates [19,21,22]. Aminoglycosides, such as streptomycin and gentamicin, tetracyclines, and the fluoroquinolone ciprofloxacin are some effective antibiotics for bubonic plague treatment [20,23,24].



**Figure 1.** *Y. pestis* infection can lead to three forms of plague. Bubonic plague can result from flea bites or handling infected animals and can result in a severe localized infected lymph node referred to as a buboe (green). Septicemic plague can result as a secondary issue arising from bubonic disease or if the bacteria are introduced directly to the blood stream (red). Pneumonic plague is the most severe form of the disease and can result in person-to-person spread if untreated and initiated by the deposition of *Y. pestis* bacteria into the respiratory tract of individuals (blue).

In other more severe cases, the bacteria can enter the blood stream directly and multiply, causing septicemic plague. The increased number of bacteria in the blood causes the release of endotoxins, leading to ischemic necrosis. In those cases, *Y. pestis* directly infects the blood without developing bubonic plague symptoms (resulting in primary septicemic plague) [25]. Furthermore, septicemia may induce intravascular coagulation that may lead to gangrene of the extremities. The prognosis for these patients is poor, with mortality rates reaching 100% in untreated individuals. Even when the appropriate treatment is administered, mortality rates remain high [26]

A third manifestation of plague, pneumonic plague, can be transmissible either person-to-person or by secondary pneumonia, resulting from the colonization of the lungs with *Y. pestis* via hematogenous spreading [1,27]. If droplets containing plague bacteria are inhaled, the result can be primary pneumonic plague. Secondary pneumonic plague may be associated with primary septicemic plague or as a complication of bubonic plague. In the United States, approximately 5–10% of patients develop secondary pneumonic plague [28]. Symptoms of plague include chills, fever, body pains, headache, weakness, dizziness, and chest discomfort [29]. These rather non-descript symptoms mirror many other infectious diseases, which can lead to frequent misdiagnosis and subsequent poor disease outcomes for the patients. Blood cultures or a sputum sample can be used to diagnose pneumonic

plague [30]. Pneumonic plague is considered highly contagious and is nearly 100% lethal if appropriate treatment is not administered within the first 20 h after onset of symptoms [30].

Due to rapid spread, high fatality rates, and the ability to transmit via aerosols, *Y. pestis* has been classified as a Tier 1 select agent by the United States Department of Health and Human Services and is considered an agent of biothreat concern [31,32]. Numerous studies have been performed in mice and other species in order to elucidate *Y. pestis* pathogenesis and pneumonic plague disease progression in animal models of human disease [25,33–35]. It has been reported that during the first 36 h post infection in mice, there is an increase in bacterial replication in the lungs with no appreciable changes in cytokines or chemokines levels [36,37]. In this pre-inflammatory phase, it has been shown that *Y. pestis* suppresses the host immune response in order to facilitate pulmonary infection [38,39]. After 36 h, the pro-inflammatory phase begins, where there is an upregulation of cytokine or chemokine levels, resulting in a critical point that can lead to death [40].

## 2. *Yersinia pestis* Virulence Plasmids

*Y. pestis* must be able to survive in and infect very diverse hosts, including both fleas and mammals. There are numerous essential virulence factors and effector proteins that are either encoded on the chromosome of *Y. pestis* or carried on its plasmids. It is believed that *Y. pestis* evolved from the genetically related *Yersinia* species *Yersinia pseudotuberculosis* (usually an intestinal pathogen) through the process of gaining plasmids, most likely several thousands of years ago [4,41,42].

*Y. pestis* carries three plasmids, two of which are unique to this species: pMT1 (or pFra), which encodes the F1 capsular antigen and pPCP (or pPst or pPla), which carries the gene for the virulence factor plasminogen activator. The third plasmid is common to the human pathogenic *Yersinia* and is known as pCD1 (calcium dependence), pYV (*Yersinia* virulence), or pLcr (low calcium response). This plasmid is responsible for the synthesis of a number of anti-host factors and is an absolute requirement for virulence.

The pMT1/pFra plasmid (100–110 kb) carries two important *Y. pestis* virulence factors involved with survival/infection of these two different hosts: the murine toxin Ymt and the F1 capsular protein. Ymt is a phospholipase D which has toxic properties for mice and rats but not for other animals [43–45]. More importantly, Ymt is required for survival within the midgut of the flea by protecting it against some components of plasma [46]. In addition, the *caf* operon encoding for the F1 capsular antigen protein (referred to here as F1) is also located on pMT1. The F1 antigen has been described both as capsular and fimbrial-like as it is composed of fibers [47–50]. The F1 protein is produced abundantly in vivo during infection of a mammal and in vitro when grown at 37 °C. F1 is thought to protect *Y. pestis* from uptake by host phagocytic cells [51]. However, naturally derived and genetically engineered F1-negative *Y. pestis* strains have been described and remain virulent in animal models of plague [52,53].

The other *Y. pestis* specific plasmid (pPCP/pPst/pPla) is 9.5 kb and carries genes that encode for pesticin, pesticin immunity protein, and plasminogen activator (Pla) [54]. Pla appears to be a multifunctional protein and belongs to the ompT family of enterobacterial surface proteins. One of the functions of Pla during infection is to cleave numerous host substrates, such as those involved in coagulation and fibrinolysis [55]. During bubonic plague, Pla activates host fibrolysis to allow bacterial dissemination from the site of infection [56,57]. Furthermore, this protein is believed to alter the host immune response during pneumonic plague to allow outgrowth of the bacteria within the lungs [58,59]. In addition to its ability to cleave proteins, it has a role in mediating bacterial adhesion to host cells and extracellular matrices [60–64].

The final plasmid is pCD1/pYV/pLcr (68–75 kb), which is common to all human pathogenic *Yersinia*, is essential for virulence, and carries genes encoding for the Type III secretion system (T3SS) and effector proteins known as Yops (*Yersinia* outer protein). The T3SS forms a syringe-like structure (injectisome) made up of 27 proteins, including the LcrV protein, which is both a structural and effector protein and is critical for virulence [65–76].

The injectisome is able to “inject” host cells when in close contact with Yops. Two of the Yops (YopB and YopD) function to transport the other six effector proteins into the host cell (YopO, YopH, YopM, YopT, YopJ, and YopE). Toxic activities of the Yops include disruption of the cytoskeleton, interference with phagocytic activity, prevention of proinflammatory cytokine synthesis, inhibition of the oxidative burst, and induction of programmed cell death (apoptosis). The overall effect of the Yops is to block phagocytic uptake of the bacteria by host macrophages and polymorphonuclear leukocytes [77–82].

### 3. Outbreak Prevention

Despite the efforts of public health agencies to monitor and prevent this disease, reports of plague outbreaks continue to exist in various parts of the world [83–85]. The United States, China, India, Vietnam, Democratic Republic of the Congo, Peru, and Madagascar are among the countries that have confirmed plague cases annually and their respective climates, public health infrastructure, surveillance programs, and socio-economic differences make outbreak prevention strategies and severity of outbreaks unique in each case [86–88]. Madagascar is currently the most affected country with the highest numbers of recently reported cases of plague, representing approximately 75% of the reported cases in the world [87,89,90]. Differences in weather and temperature patterns affect the abundance of fleas [89,91] which in turn influences the start of annual transmission that generally arises between the months of September to April in Madagascar [92]. Given the right conditions, it may be possible for person-to-person transmission mediated by human ectoparasites—especially in underdeveloped but densely populated areas [93]. A total of 2417 suspect plague cases, including 209 deaths, were reported by the World Health Organization (WHO) from August to November in 2017 in Madagascar [94]. Generally, bubonic plague cases in Madagascar are commonly concentrated in rural areas, while pneumonic cases are more prevalent in urban locations [95]. In 2017, the majority (77%; 1854 total) reported were clinically classified as pneumonic plague whereas 15% (355) were classified as bubonic plague. Only one of the reported cases was diagnosed as septicemic plague while the remaining 207 cases remain unclassified [94]. Control and prevention of plague cases in Madagascar has proven to be challenging. Most of the prevention strategies are focused on the rodent host and the flea vectors [91]. Inappropriate use of chemical insecticides inadvertently selects for flea resistance, which leads to the survival of *Y. pestis*-infected fleas [91]. Food handling/storage procedures, community sanitation standards, and environmental factors of the household and its surroundings are parameters that can increase human interactions with rodent reservoirs [96]. Importantly, distribution of supplies and equipment including hand washing facilities, sanitation standards, disinfectants (e.g., laundry soap, chlorine powder, disinfectant sprays), and personal protective equipment contribute to an efficient plague prevention strategy [94].

### 4. Current Antibiotic Therapies

Due to the rapid onset and rather non-descript disease characteristics of plague, the key to positive patient outcomes, particularly after infection with aerosolized bacteria, is early diagnosis and rapid implementation of appropriate medical countermeasures. The gold-standard for plague diagnostics continues to be culture-positive samples (normally blood or sputum samples) but other molecular diagnostic assays have been used or continue to be developed [2].

If diagnosed accurately and early after infection, human plague cases can be controlled by the appropriate administration of antimicrobial drugs, including aminoglycoside, tetracyclines, fluoroquinolones, and sulfonamides [91,97–101]. Generally, successful treatment of *Y. pestis* infections requires early recognition and the administration of an effective antibiotic during the first 24 h after the onset of symptoms that often present within 24 to 48 h post-infection [18]. According to the United States Centers for Disease Control and Prevention (CDC), the majority of human plague cases can be treated successfully with antibiotics [18]. The most effective antibiotics against *Y. pestis* are aminoglycosides, such

as streptomycin and gentamicin, and accordingly, streptomycin is the first-line antibiotic for treatment of plague in most cases; both can be administered and are recommended for all adults, including pregnant women, immunocompromised patients, and children (although reduced dosages may be warranted in some cases) [102]. Chloramphenicol is another suitable agent for bubonic or septicemic plague and can be administered in conjunction with aminoglycosides [18,102]. Doxycycline and tetracycline are acceptable alternate antimicrobial agents as primary treatment for patients with uncomplicated plague and can also be used in conjunction with other antibiotics or in patients intolerant of aminoglycosides [18]. Fluoroquinolones, such as ciprofloxacin, have been demonstrated to have pharmacokinetic properties that make them suitable for plague therapy. Ciprofloxacin possesses bactericidal activity and its efficacy has been tested in vitro, in vivo, and in patients with bubonic plague [103,104]. Individuals in close contact with people afflicted with pneumonic plague, exposed to *Y. pestis* infected fleas, or who have been handling body fluids or tissues infected with *Y. pestis* should receive prophylactic antibiotic therapy.

The emergence of multidrug-resistant (MDR) strains of bacterial pathogens, including *Y. pestis*, is one of the most critical issues facing public health due to the difficulty in treatment, the high cost associated with medical care (particularly in developing countries) and increased mortality rates associated with the drug-resistant phenotypes [105]. This increased incidence of antibiotic resistance is likely due to the close proximity between humans and rodents, the extensive use of antibiotics in animal husbandry, and/or the presence of antibiotics in contaminated hospital waste. In addition to being the most recent epicenter of plague infections, Madagascar is also a focus for MDR *Y. pestis* strains. In 1995, two different strains of naturally occurring antibiotic-resistant *Y. pestis* were isolated in Madagascar. The first one, *Y. pestis* 17/95 was isolated from a 16-year-old boy, and the second strain 16/95 was isolated from a 14-year-old boy; both cases were diagnosed with bubonic plague [97,106,107]. Galimand et al. determined that strain 17/95 isolated from the city of Ambalavao was resistant to eight antimicrobial agents, including those for therapy and prophylaxis—while strain 16/95, isolated from the city of Ambohimahaso, demonstrated high levels of streptomycin-resistance [97,106]. The multiple antibiotic resistance genes in both MDR strains of *Y. pestis* were all located on plasmids belonging to different incompatibility (Inc) groups [108]. *Y. pestis* strain 17/95 encoded MDR genes on pIP1202 in the Inc6-C group of plasmids, while *Y. pestis* strain 16/95 harbored MDR genes on pIP1203, which belongs to the IncP group of plasmids [97]. In 1998, a novel doxycycline-resistant strain was isolated from the spleen of a rat (*Rattus norvegicus*) in Antananavo, Madagascar [109]. To date, these characterized MDR *Y. pestis* strains were isolated from distinct hosts, at different times, and from distant locations [109]. In addition, Cabanel, et al., 2018 cited that independent horizontal transfer may be the reason for unrelated plasmids among these MDR strains. Other drug-resistant strains and antimicrobial resistance mechanisms have been reported and all aspects of drug-resistance in *Y. pestis* must remain an important research priority [110,111].

## 5. Vaccines

Due to the relative ease of transmissibility, rapid course of disease, non-descript clinical signs and symptoms, high mortality, and antibiotic resistance potential, effective vaccine strategies are needed. An effective and safe plague vaccine is important from a public health perspective but also in context of national biodefense strategies [2,33,112,113]. The first plague vaccines, developed late in the 19th century, consisted of killed whole cells of *Y. pestis* [114].

An immunogenic and somewhat less-reactogenic licensed vaccine (USP) containing a formalin-killed highly virulent 195/P strain of *Y. pestis*, was effective in preventing or ameliorating bubonic disease, as seen by the low incidence of plague cases in military personnel serving in Vietnam. However, the extent of efficacy remains in question, and it is thought that the protection was almost entirely based upon titers to the F1 capsular antigen [115–118]. In vivo data suggested that this vaccine might not offer optimal

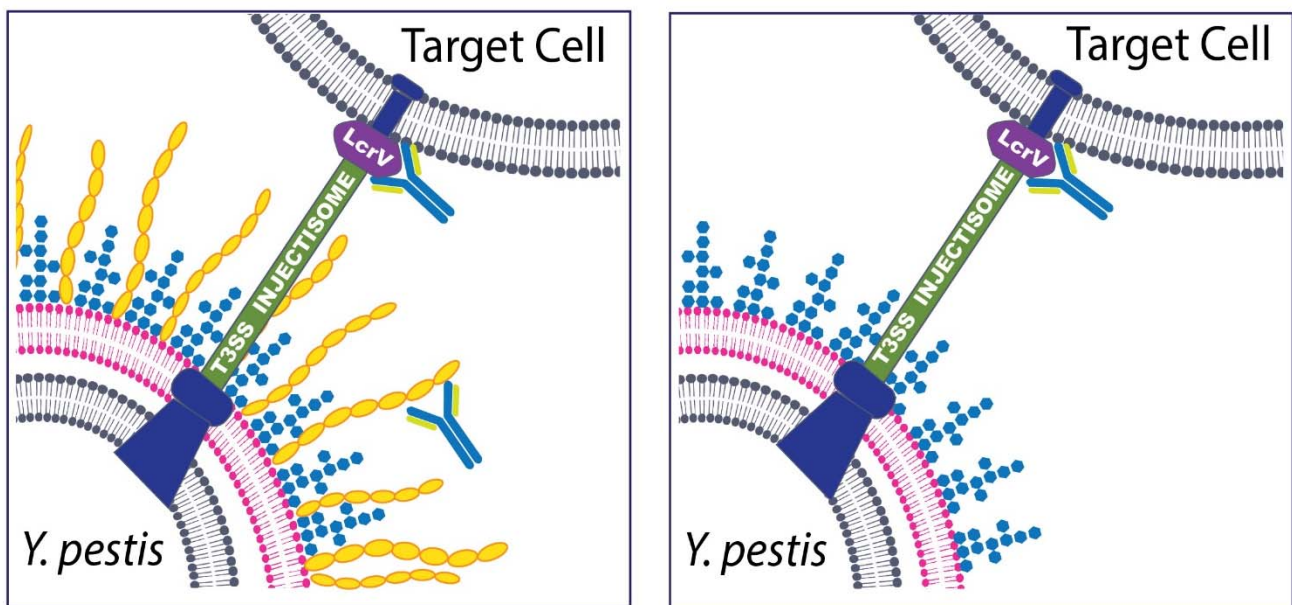
protection against pneumonic plague [119–125]. Such vaccines may not protect against genetically engineered or naturally occurring F1-negative strains, which often maintain significant virulence despite the loss of capsule. The killed whole-cell preparation vaccines, in the absence of frequent boosting, failed to provide long-term protection against bubonic plague.

Live bacterial vaccines are protective, and in many cases, contain a nearly complete array of native antigens—thereby reducing the chances of breakthrough infections. However, live attenuated vaccines are also considered more reactogenic than other vaccination approaches, and may cause safety concerns in certain subsections of the community (e.g., elderly or immune-compromised), and depending upon the vaccination strategy may elicit only short-term immunity [114]. Candidate live vaccines have included recombinant *Y. pestis*, *Y. pseudotuberculosis*, and *Salmonella* strains [126–128].

Live attenuated *Y. pestis* vaccines, such as the EV strain (derived and attenuated in the 1920s by serial passaging a virulent *Y. pestis* parent strain isolated from a patient identified as EV), have been in use in various parts of the world for decades [129]. Evidence demonstrated that these live vaccine strategies were able to protect against pneumonic and bubonic plague and induced high antibody titers [119,130]. Unfortunately, these vaccines may have severe side effects and systemic reactions in non-human primates [119] and humans [131], and only induce short-lived protection that require annual boosters [132,133].

Recently, additional live attenuated vaccine strategies using attenuated *Y. pestis* strains are also being developed and their corresponding immune responses evaluated [134,135]. Bubeck and Dube achieved significant protection when using a  $\Delta yopH$  live vaccine strain [136] and Bozue et al., demonstrated that a *Y. pestis*  $\Delta yscN$  mutant strain also offered significant protection against challenge with a fully virulent strain of *Y. pestis* [134,137]. Follow-on studies further characterized the vaccine potential of  $\Delta yscN$  strains of *Y. pestis* as well as a strain lacking both the pigmentation (*pgm*) locus and the pPst virulence plasmid [138–141]. In addition, promising results were obtained with *Y. pseudotuberculosis* based live vaccines that conferred protection and immunological memory [142–145].

Besides whole-cell based vaccines, considerable work on subunit vaccine strategies has been completed. With recombinant DNA technology and improved protein chemistry, antigens can be purified for subunit vaccine development. Protein-based subunit vaccines have the potential of increased stability and consistency between vaccine preparations along with reduction in adverse effects that are often correlated with live vaccines [146]. Both the United States and the United Kingdom have focused attention on the development of subunit vaccines based on the fraction 1 (F1) capsular antigen and the low calcium response protein V (LcrV) antigens [123,147,148] (Figure 2). As discussed earlier, *Y. pestis* expresses a capsule antigen F1, encoded by the *cafI* gene, which has been shown to have significant anti-phagocytic activity [51,149–153]. LcrV is a secreted virulence protein which is essential for survival in the host, acting as an immunosuppressive factor [65]. Early work demonstrated a protective effect associated with active vaccination with V fractions [154–157]. Several groups reported that anti-V antibodies may be protective by promoting phagocytosis of bacteria and reducing bacteria-induced cytotoxicity [158–160]. In addition to being a protective antigen, LcrV was later shown to be a multi-factorial protein that is an important structural component of the T3SS (injectisome) and a secreted protein that is trafficked into eukaryotic cells; furthermore, the LcrV antigen can regulate aspects of the host immune response extracellularly by induction of anti-inflammatory IL-10 [65–76,156]. Unfortunately, important differences have been documented between LcrV proteins isolated from various *Y. pestis* strains which may hamper protective efficacy of subunit vaccines that rely on a specific polymorph for induction of immunological protection but may have a limited cross-reactive response [161]. Nevertheless, both F1 and V have been studied as components of subunit vaccines and have been shown to confer significant protection against bubonic and pneumonic plague induced by encapsulated strains of *Y. pestis*, with few documented concerns about tolerability or safety [155,157,162–165].



**Figure 2.** Schematic of Antibodies that target *Y. pestis* and are effective at ameliorating disease. *Y. pestis* is a Gram-negative bacterium that expresses multiple potential targets that have been exploited for the development of novel medical countermeasures. Antibodies generated by active vaccination or administered via passive immunization have been successful at protecting cell culture and animals from *Y. pestis* infection. These targets include The F1 capsular antigen (yellow structures depicted in the left panel) and the LcrV (V antigen) component of the T3SS injectisome. The capsule, while not absolutely necessary for virulence, has been the target of both vaccine and therapeutic strategies. The LcrV protein has been shown to be essential for virulence and has been a successful target in both active and passive immunization studies and is often combined with the F1 capsular antigen (i.e., the F1-V vaccine or mAb cocktail experiments). (Left Panel) In most cases, the *Y. pestis* bacterium will interact directly with host target cells via the T3SS injectisome and a robust anti-phagocytic capsule will also be present; thus, both anti-F1 and anti-V antibodies are potentially effective. (Right Panel) Non-encapsulated strains of *Y. pestis* can be found in nature or engineered in the laboratory. In cases of infection caused by non-encapsulated *Y. pestis*, the antibodies to the F1 capsular antigen are no longer effective and the protective immune response generated by a vaccine or the effective therapeutic mAb relies solely on the anti-V antibodies. A lipopolysaccharide structure (LPS) often observed in *Y. pestis* grown at 37 °C is depicted in blue in both panels. Other protective antigens have been identified and other novel antigen targets will almost certainly be identified in ongoing research efforts.

The primary subunit vaccine candidate in the United States is the recombinant F1-V, a fusion protein of the F1 capsular antigen and the *lcrV* gene product [166–170]. The United Kingdom pursued a similar strategy for vaccination but retained the F1 and V immunogens as separate proteins [171–173]. PharmAthene further advanced this concept and developed a recombinant dual antigen vaccine for plague, composed of rF1 + rV, named RypVax™ [174,175]. A truncated LcrV antigen, rV10, developed by Schneewind and colleagues in 2011 was also assessed [176]. Both vaccines, rF1 + rV and rV10, were tested and demonstrated efficacy against pneumonic plague infection in mice, guinea pigs and *Cynomolgus* macaques [176,177] but not in African green monkeys [125]. Further investigations of enhancing immunogenicity or delivery of these subunit vaccines have been attempted or are ongoing by several groups [178–185].

The two-component vaccines have been variably effective and are vulnerable to breakthrough infection. Researchers found that the combination of these subunits significantly enhances protection against bubonic and pneumonic plague in different animal models [176,186,187]. The protection afforded by this vaccine strategy against F1-negative strains relies entirely on the LcrV antigen component of the F1-V fusion protein. Since there is evidence for V heterogeneity within *Yersinia* species, the potential exists that naturally occurring or engineered strains harboring altered LcrV antigens could overcome F1-V-induced immunity [161].

Other vaccine strategies have attempted to identify vaccine antigens that would protect animals against non-encapsulated strains. Andrews demonstrated that active vaccination against YopD could protect mice against an F1-negative strain of *Y. pestis* [188]. Later studies by Ivanov et al. further characterized the protective efficacy of YopD and created fusion proteins of YopBD and YopBDE [189]. Ivanov et al. achieved protection with both active and passive vaccination strategies using these proteins, but these data suggested that anti-Yop immune responses were most protective against non-encapsulated *Y. pestis* [189]. While there has been progress in vaccine development, the need remains for other reliably protective and readily deployable countermeasures against plague.

## 6. Antibodies

There has been significant interest in and effort towards identifying antibody therapies in animal models of plague. In 1963, Lawton and coworkers identified protection associated with anti-LcrV polyclonal serum passively administered to mice. Importantly, it was determined that the protection associated with this polyclonal serum could not be completely attributable to the LcrV antigen due to the likelihood of other *Yersinia* proteins present in the material used to generate the sera [190]. Later, Motin et al. demonstrated with more modern techniques that a highly purified preparation of the V protein could be produced and used for polyclonal sera generation [190]. These anti-sera directed against native LcrV antigen or recombinant LcrV antigens were able to provide substantial passive protection against *Y. pestis* infection.

Tables 1 and 2 and the following paragraphs provide summary information extracted from noteworthy publications describing particularly effective monoclonal antibodies in mouse models of plague. Hill et al. demonstrated that a monoclonal antibody directed against the LcrV could protect against a fully virulent strain of *Y. pestis* and went on to demonstrate which regions of the LcrV antigen appeared to be protective epitopes [156]. Quenee et al. and Amemiya et al. further elaborated on the importance of the specific binding sites on protective anti-LcrV monoclonal antibodies [191,192]. The mAb 7.3 was shown to protect macrophages from *Y. pestis*-induced cell death and also to promote phagocytosis of the bacteria [158,193]. Importantly, much of the protection afforded by mAb 7.3 can be attributed to the blocking of the T3SS machinery. When anti-V antibodies block this injectisome, the immunomodulation and anti-phagocytic Yop effectors are not efficiently secreted, thus blocking cytotoxic phenotypes and promoting phagocytosis of the bacterial cells [158]. This concept was further supported by Eisele and Anderson when they demonstrated that both blocking the T3SS as well as inducing phagocytosis are required from an anti-LcrV mAb in order to optimally protect against pneumonic plague in a mouse model of disease [194]. Novel Adenovirus-mediated delivery has also been used to demonstrate the protection associated with anti-LcrV antigen mAbs [195].

Partly due to the known heterogeneity amongst LcrV protein sequences from different bacterial isolates [161,196–198], a multi-antigen strategy was postulated to be required to optimize protection. Anderson et al. also demonstrated that it was possible to passively protect mice against either bubonic or pneumonic plague [199] with anti-F1 antibodies. These anti-F1 monoclonal antibodies, however, would not protect against F1-negative (non-encapsulated) strains of *Y. pestis* (Figure 2). Since immunity to F1 is not sufficient to protect in all cases, there was renewed focus on the incorporation of the LcrV antigen or other proteins for multifactorial strategies.



**Table 1.** Monoclonal antibodies shown to protect mice in bubonic plague models (subcutaneous challenge with bacteria).

Antigen <sup>a</sup>	mAb Description	Antibody/Therapeutic Administration			<i>Y. pestis</i> Challenge Strain <sup>d</sup>	Challenge Dose (LD <sub>50</sub> )	Ref.
		Route	Concentration	Schedule			
F1; LcrV; F1V + LcrV	human IgG1	IP	500 µg	24 h pre–120 h post	CO92	25–40	202
LcrV	mouse	IP	350 µg	24 h pre	GB	12	156
LcrV <sup>b</sup>	mouse IgG1, IgG2a	IP	1–500 µg	24 h pre	CO92 or C12	21–39	192
LcrV; F1 + LcrV	mouse IgG1	IP	0.7–100 µg	4 h pre–96 post	GB	9.6–91,000	200
LcrV	mouse IgG1	IP	200 µg	1 h pre	CO92	20	191
F1 <sup>c</sup>	mouse IgG1	IP	125–500 µg	6 h or 24 h pre	CO92	48–54	199
F1	not reported	IV	100 µg	24 h pre	141	600	203

a, unless otherwise noted mAbs tested in BALB/c female mice; b, tested in BALB/c and Swiss Webster mice; c, tested in Swiss Webster female mice; d, bacteria delivered via subcutaneous injection.

**Table 2.** Monoclonal antibodies shown to protect mice in pneumonic plague models (intranasal instillation or exposure to aerosolized bacteria).

Antigen <sup>a</sup>	mAb Description	Antibody/Therapeutic Administration			<i>Y. pestis</i> Challenge Strain <sup>f</sup>	Challenge Dose (LD <sub>50</sub> )	Ref.
		Route	Concentration	Schedule			
LcrV	mouse IgG1	IP	35 µg	4 h pre–96 h post	GB	88	156
LcrV <sup>b</sup>	mouse IgG1	IP	200 or 400 µg	1 h pre	CO92 <sup>g</sup>	15–20	194
LcrV <sup>c</sup>	mouse IgG2b	IP, IV	100–500 µg, 10 <sup>11</sup> pu <sup>e</sup>	94 h pre–24 h post	CO92 <sup>g</sup>	363–9080	195
F1 <sup>d</sup>	mouse IgG1	IP	125–500 µg	6 h or 24 h pre	CO92	29–74	199
F1 + LcrV	mouse IgG1	IT	77.5 µg (each)	2 h post	GB	27	200

a, unless otherwise noted mAbs tested in BALB/c female mice; b, tested in C57BL/6 female mice; c, tested in BALB/c female and C57BL/6 male mice; d, tested in Swiss Webster female mice; e, antibodies delivered as hybridoma supernatant or via adenovirus vector; f, unless otherwise noted aerosolized bacteria were delivered; g, intranasal instillation was used for challenge

Combinations of F1 and LcrV monoclonal antibodies were shown to protect mice against both bubonic and pneumonic plague either prophylactically or as post-exposure therapy [200,201]. More recent efforts have continued to examine strategies combining anti-F1 and anti-LcrV antibodies [202]. Xiao et al. identified three human mAbs: m252 for anti-F1, and m253 and m254 for anti-LcrV. They found that anti-F1 human mAb (m252) provided better protection in mice than anti-LcrV human mAbs. However, an apparent synergistic effect was found when they combined all three antibodies. Another three anti-F1 (F5C10, F6E5, and F2H5) mAbs were tested against subcutaneous challenge with *Y. pestis* 141 and showed different protection levels. Liu et al. demonstrated that mAb F2H5 from a mouse hybridoma provides complete protection from bubonic plague in BALB/c mice [203]. Altogether, it would be feasible that these mAbs against F1 or LcrV can be utilized as a potential treatment or prophylaxis for humans against plague. Additional anti-*Y. pestis* human antibodies have recently been produced and are currently being evaluated for therapeutic application [204].

## 7. Advantages of Monoclonal Antibodies (mAbs) and Final Perspectives

Currently, there are only a few mAbs licensed for use against bacterial infectious agents. To date, mAb against *Clostridium difficile* and *Bacillus anthracis* toxins are licensed in Europe and the USA [205–207]. Other work has focused on mAbs against *Staphylococcus aureus* or *Pseudomonas aeruginosa* [208]. The renewal of interest in mAb therapies is even

more relevant given the current era of worrisome multidrug resistance in bacterial isolates of clinical importance. Several clinically relevant bacteria such as *Burkholderia pseudomallei* and *Burkholderia mallei* are naturally resistant to many antibiotics [209]. Examples of emerging MDR bacteria include but are not limited to *S. aureus*, *C. difficile*, *P. aeruginosa*, *Acinetobacter baumannii*, *Enterococci*, etc [210–213]. This MDR trait has been observed with *Y. pestis*, and the lack of effective therapies for such an infection could result in catastrophic loss of life, whether from a naturally emerging outbreak or an intentional attack utilizing purposefully engineered bacteria.

Recent strategies have focused on nimble and rapid platforms that can be leveraged when combatting outbreaks and emerging threats. Advances in rapid mAb discovery, optimization, and production make this an attractive strategy that could significantly decrease the time required to get a product to civilian populations in the midst of an outbreak or to military personnel deployed to areas where endemic disease could be an issue and an effective vaccine has yet to be identified. Other more novel strategies involve administering nucleic acids that encode the protective mAb to patients. In that case, a nucleic acid encoding the immunoglobulin may be manufactured or obtained from a cDNA library or nucleic acid isolated from any tissue or cells expressing the antibody. These nucleic acids can be cloned into a suitable vector and administered into an infected patient [202].

These concepts have been useful recently during West African Ebola virus outbreaks [214]. In this epidemic, mAbs were demonstrated to be important novel treatment strategies. Products such as ZMapp® and others were critical in the response to the Ebola virus epidemic [214]. Viruses of recent or continual concern including HIV, Zika, and COVID-19 have also been targets of these novel strategies [215–220]. Monoclonal antibodies will likely be of the utmost importance moving forward when developing novel medical countermeasures against existing and rapidly emerging infectious diseases.

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## References

1. Pechous, R.D.; Sivaraman, V.; Stasulli, N.M.; Goldman, W.E. Pneumonic plague: The darker side of *Yersinia pestis*. *Trends Microbiol.* **2016**, *24*, 190–197. [[CrossRef](#)] [[PubMed](#)]
2. Demeure, C.E.; Dussurget, O.; Fiol, G.M.; Le Guern, A.S.; Savin, C.; Pizzarro-Cerdá, J. *Yersinia pestis* and plague: An updated view on evolution, virulence determinants, immune subversion, vaccination, and diagnostics. *Genes Immun.* **2019**, *20*, 357–370. [[CrossRef](#)] [[PubMed](#)]
3. Stenseth, N.C.; Atshabar, B.B.; Begon, M.; Belmain, S.R.; Bertherat, E.; Carniel, E.; Gage, K.L.; Leirs, H.; Rahalison, L. Plague: Past, present, and future. *PLoS Med.* **2008**, *5*, e3. [[CrossRef](#)] [[PubMed](#)]
4. Achtman, M.; Zurth, K.; Morelli, G.; Torrea, G.; Guiyoule, A.; Carniel, E. *Yersinia pestis*, the cause of plague, is a recently emerged clone of *Yersinia pseudotuberculosis*. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 14043–14048. [[CrossRef](#)]
5. Glatter, K.A.; Finkelman, P. History of the plague: An ancient pandemic for the age of COVID-19. *Am. J. Med.* **2021**, *134*, 176–181. [[CrossRef](#)]
6. Brubaker, R.R. *Yersinia pestis*. *Mol. Med. Microbiol.* **2015**, *3*, 1845–1865.
7. Frith, J. The history of plague—Part 1. The three great pandemics. *J. Mil. Vet. Health* **2012**, *20*, 11–16.
8. Barbieri, R.; Signoli, M.; Chev e, D.; Costedoat, C.; Tzortzis, S.; Aboudharam, G.; Raoult, D.; Drancourt, M. *Yersinia pestis*: The natural history of plague. *Clin. Microbiol. Rev.* **2020**, *34*, e00044–19. [[CrossRef](#)]
9. Drancourt, M.; Raoult, D. Molecular history of plague. *Clin. Microbiol. Infect.* **2016**, *22*, 911–915. [[CrossRef](#)]
10. Bramanti, B.; Dean, K.R.; Wall e, L.; Stenseth, N.C. The third plague pandemic in Europe. *Proc. Biol. Sci.* **2019**, *286*, 20182429. [[CrossRef](#)]
11. Eisen, R.J.; Gage, K.L. Adaptive strategies of *Yersinia pestis* to persist during inter-epizootic and epizootic periods. *Vet. Res.* **2009**, *40*, 1. [[CrossRef](#)] [[PubMed](#)]

12. Raoult, D.; Mouffok, N.; Bitam, I.; Piarroux, R.; Drancourt, M. Plague: History and contemporary analysis. *J. Infect.* **2013**, *66*, 18–26. [[CrossRef](#)] [[PubMed](#)]
13. Melman, S.D.; Ettestad, P.E.; VinHatton, E.S.; Ragsdale, J.M.; Takacs, N.; Onischuk, L.M.; Leonard, P.M.; Master, S.S.; Lucero, V.S.; Kingry, L.C. Human case of bubonic plague resulting from the bite of a wild Gunnison's prairie dog during translocation from a plague-endemic area. *Zoonoses Public Health* **2018**, *65*, e254–e258. [[CrossRef](#)]
14. Dai, R.; Wei, B.; Xiong, H.; Yang, X.; Peng, Y.; He, J.; Jin, J.; Wang, Y.; Zha, X.; Zhang, Z.; et al. Human plague associated with Tibetan sheep originates in marmots. *PLoS Negl. Trop. Dis.* **2018**, *12*, e0006635. [[CrossRef](#)]
15. Richgels, K.L.; Russell, R.E.; Bron, G.M.; Rocke, T.E. Evaluation of *Yersinia pestis* transmission pathways for sylvatic plague in prairie dog populations in the Western U.S. *Ecohealth* **2016**, *13*, 415–427. [[CrossRef](#)] [[PubMed](#)]
16. CDC. Fatal laboratory-acquired infection with an attenuated *Yersinia pestis* Strain—Chicago, Illinois, 2009. *MMWR Morb. Mortal. Wkly. Rep.* **2011**, *60*, 201–205.
17. Worsham, P.L.; McGovern, T.W.; Vietri, N.J.; Friedlander, A.M.; Bozue, J. Plague. In *Textbook of Military Medicine: Medical Aspects of Biological Warfare*; Bozue, J.A., Cote, C.K., Glass, P.J., Eds.; Borden Institute US Army Medical Department Center and School Health Readiness Center of Excellence: Houston, TX, USA, 2018; pp. 247–284.
18. Yang, R. Plague: Recognition, treatment, and prevention. *J. Clin. Microbiol.* **2017**, *56*, e01519-17. [[CrossRef](#)] [[PubMed](#)]
19. Nikiforov, V.V.; Gao, H.; Zhou, L.; Anisimov, A. Plague: Clinics, diagnosis and treatment. *Adv. Exp. Med. Biol.* **2016**, *918*, 293–312.
20. Dennis, D.T.; Gage, K.L.; Gratz, N.G.; Poland, J.D.; Tikhomirov, E. *Plague Manual: Epidemiology, Distribution, Surveillance and Control*; No. WHO/CDS/CSR/EDC/99.2; World Health Organization: Geneva, Switzerland, 1999.
21. Sebbane, F.; Lemaitre, N. Antibiotic therapy of plague: A review. *Biomolecules* **2021**, *11*, 724. [[CrossRef](#)]
22. Bossi, P.; Tagnell, A.; Baka, A.; Looock, F.V.; Hendriks, J.; Werner, A.; Maidhof, H.; Gouvras, G. Bichat guidelines for the clinical management of plague and bioterrorism-related plague. *Euro Surveill* **2004**, *9*, E5–E6. [[CrossRef](#)]
23. Lemaitre, N.; Ricard, I.; Pradel, E.; Foligné, B.; Courcol, R.; Simonet, M.; Sebbane, F. Efficacy of ciprofloxacin-gentamicin combination therapy in murine bubonic plague. *PLoS ONE* **2012**, *7*, e52503. [[CrossRef](#)]
24. Boulanger, L.L.; Ettestad, P.; Fogarty, J.D.; Dennis, D.T.; Romig, D.; Mertz, G. Gentamicin and tetracyclines for the treatment of human plague: Review of 75 cases in New Mexico, 1985–1999. *Clin. Infect. Dis.* **2004**, *38*, 663–669. [[CrossRef](#)]
25. Lawrenz, M.B. Model systems to study plague pathogenesis and develop new therapeutics. *Front. Microbiol.* **2010**, *1*, 119. [[CrossRef](#)]
26. Dillard, R.L.; Juergens, A.L. *Plague*; StatPearls: Treasure Island, FL, USA, 2020.
27. Cleri, D.J.; Marton, R.; Rabbat, M.; Vernaleo, J. *Pneumonia Caused by Yersinia pestis: Plague Pneumonia, in Community-Acquired Pneumonia*; Marrie, T.J., Ed.; Springer: Boston, MA, USA, 2001; pp. 777–799.
28. Kool, J. Risk of person-to-person transmission of pneumonic plague. *Clin. Infect. Dis.* **2005**, *40*, 1166–1172. [[CrossRef](#)] [[PubMed](#)]
29. Dennis, D.T.; Mead, P.S. Plague. *Trop. Infect. Dis.* **2006**, *1*, 471–481.
30. Gage, K.L.; Beard, C.B. 126—Plague. In *Infectious Diseases*, 4th ed.; Cohen, J., Powderly, W.G., Opal, S.M., Eds.; Elsevier: Amsterdam, The Netherlands, 2017; pp. 1078–1084.e1.
31. Wagar, E. Bioterrorism and the role of the clinical microbiology laboratory. *Clin. Microbiol. Rev.* **2016**, *29*, 175–189. [[CrossRef](#)] [[PubMed](#)]
32. Ansari, I.; Grier, G.; Byers, M. Deliberate release: Plague—A review. *J. Biosaf. Biosecur.* **2020**, *2*, 10–22. [[CrossRef](#)]
33. Du, Z.; Wang, X. Pathology and pathogenesis of *Yersinia pestis*. *Adv. Exp. Med. Biol.* **2016**, *918*, 193–222.
34. Hewitt, J.A.; Lanning, L.L.; Campbell, J.L. The African green monkey model of pneumonic plague and US Food and Drug Administration approval of antimicrobials under the animal rule. *Clin. Infect. Dis.* **2020**, *70* (Suppl. S1), S51–S59. [[CrossRef](#)]
35. Warren, R.; Lockman, H.; Barnewall, R.; Krile, R.; Bermeo Blanco, O.; Vasconcelos, D.; Price, J.; House, R.V.; Bolanowski, M.A.; Fellows, P. *Cynomolgus macaque model for pneumonic plague*. *Microb. Pathog.* **2011**, *50*, 12–22. [[CrossRef](#)]
36. Bubeck, S.S.; Cantwell, A.M.; Dube, P.H. Delayed inflammatory response to primary pneumonic plague occurs in both outbred and inbred mice. *Infect. Immun.* **2007**, *75*, 697–705. [[CrossRef](#)]
37. Lathem, W.W.; Crosby, S.D.; Miller, V.L.; Goldman, W.E. Progression of primary pneumonic plague: A mouse model of infection, pathology, and bacterial transcriptional activity. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 17786–17791. [[CrossRef](#)]
38. 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*, e1003679. [[CrossRef](#)]
39. Banerjee, S.K.; Crane, S.D.; Pechous, R.D. A dual role for the plasminogen activator protease during the preinflammatory phase of primary pneumonic plague. *J. Infect. Dis.* **2020**, *222*, 407–416. [[CrossRef](#)] [[PubMed](#)]
40. Pechous, R.D.; Broberg, C.A.; Stasulli, N.M.; Miller, V.L.; Goldman, W.E. In vivo transcriptional profiling of *Yersinia pestis* reveals a novel bacterial mediator of pulmonary inflammation. *mBio* **2015**, *6*, e02302-14. [[CrossRef](#)] [[PubMed](#)]
41. Zhou, D.; Yang, R. Molecular Darwinian evolution of virulence in *Yersinia pestis*. *Infect. Immun.* **2020**, *77*, 2242–2250. [[CrossRef](#)]
42. Skurnik, M.; Peippo, A.; Ervelä, E. Characterization of the O-antigen gene clusters of *Yersinia pseudotuberculosis* and the cryptic O-antigen gene cluster of *Yersinia pestis* shows that the plague bacillus is most closely related to and has evolved from *Y. pseudotuberculosis* serotype O:1b. *Mol. Microbiol.* **2000**, *37*, 316–330. [[CrossRef](#)] [[PubMed](#)]
43. Rudolph, A.E.; Stuckey, J.A.; Zhao, Y.; Matthews, H.R.; Patton, W.A.; Moss, I.; Dixon, J.E. Expression, characterization, and mutagenesis of the *Yersinia pestis* murine toxin, a phospholipase D superfamily member. *J. Biol. Chem.* **1999**, *274*, 11824–11831. [[CrossRef](#)]

44. Schar, M.; Meyer, K.F. Studies on immunization against plague. XV. The pathophysiological action of the toxin of *Pasteurella pestis* in experimental animals. *Schweiz Z Pathol. Bakteriolog.* **1956**, *19*, 51–70.
45. Bergdoll, M.S.; Enterotoxins, T.C.; Montie, S.J.A. *Microbial Toxins*; Academic Press: New York, NY, USA, 1970; Volume 3, pp. 265–326.
46. Hinnebusch, B.J.; Rudolph, A.E.; Cherepanov, P.; Dixon, J.E.; Schwan, T.G. Role of *Yersinia murine* toxin in survival of *Yersinia pestis* in the midgut of the flea vector. *Science* **2002**, *296*, 733–735. [[CrossRef](#)]
47. Chen, T.H.; Crocker, T.T.; Meyer, K.F. Electron microscopic study of the extracellular materials of *Pasteurella pestis*. *J. Bacteriol.* **1956**, *72*, 851–857.
48. Davis, K.J.; Fritz, D.L.; Pitt, M.L.; Welkos, S.L.; Worsham, P.L.; Friedlander, A.M. Pathology of experimental pneumonic plague produced by fraction 1-positive and fraction 1-negative *Yersinia pestis* in African green monkeys (*Cercopithecus aethiops*). *Arch. Pathol. Lab. Med.* **1996**, *120*, 156–163.
49. Engelsberg, E.; Levy, J.B. Studies on immunization against plague. VI. Growth of *Pasteurella pestis* and the production of the envelope and other soluble antigens in a casein hydrolyzate mineral glucose medium. *J. Bacteriol.* **1954**, *67*, 438–449. [[CrossRef](#)]
50. Runco, L.M.; Myrczek, S.; Bliska, J.B.; Thanassi, D.G. Biogenesis of the fraction 1 capsule and analysis of the ultrastructure of *Yersinia pestis*. *J. Bacteriol.* **2008**, *190*, 3381–3385. [[CrossRef](#)]
51. Du, Y.; Rosqvist, R.; Forsberg, Å. Role of fraction 1 antigen of *Yersinia pestis* in inhibition of phagocytosis. *Infect. Immun.* **2002**, *70*, 1453. [[CrossRef](#)] [[PubMed](#)]
52. Welkos, S.L.; Davis, K.M.; Pitt, L.M.; Worsham, P.L.; Friedlander, A.M. Studies on the contribution of the F1 capsule-associated plasmid pFra to the virulence of *Yersinia pestis*. *Contrib. Microbiol. Immunol.* **1995**, *13*, 299–305. [[PubMed](#)]
53. Winter, C.C.; Cherry, W.B.; Moody, M.D. An unusual strain of *Pasteurella pestis* isolated from a fatal human case of plague. *Bull. World Health Organ.* **1960**, *23*, 408–409.
54. Sebbane, F.; Uversky, V.N.; Anisimov, A.P. *Yersinia pestis* plasminogen activator. *Biomolecules* **2020**, *10*, 1554. [[CrossRef](#)] [[PubMed](#)]
55. Caulfield, A.J.; Lathem, W.W. Substrates of the plasminogen activator protease of *Yersinia pestis*. *Adv. Exp. Med. Biol.* **2012**, *954*, 253–260.
56. Degen, J.L.; Bugge, T.H.; Goguen, J.D. Fibrin and fibrinolysis in infection and host defense. *J. Thromb. Haemost.* **2007**, *5* (Suppl. S1), 24–31. [[CrossRef](#)]
57. Sodeinde, O.A.; Subrahmanyam, Y.V.; Stark, K.; Quan, T.; Bao, Y.; Goguen, J.D. A surface protease and the invasive character of plague. *Science* **1992**, *258*, 1004–1007. [[CrossRef](#)]
58. Caulfield, A.J.; Walker, M.E.; Giolda, L.M.; Lathem, W.W. The Pla protease of *Yersinia pestis* degrades fas ligand to manipulate host cell death and inflammation. *Cell Host Microbe* **2014**, *15*, 424–434. [[CrossRef](#)]
59. Lathem, W.W.; Price, P.A.; Miller, V.L.; Goldman, W.E. A plasminogen-activating protease specifically controls the development of primary pneumonic plague. *Science* **2007**, *315*, 509–513. [[CrossRef](#)]
60. Kienle, Z.; Emödy, L.; Svanborg, C.; O’Toole, P.W. Adhesive properties conferred by the plasminogen activator of *Yersinia pestis*. *J. Gen. Microbiol.* **1992**, *138*, 1679–1687. [[CrossRef](#)]
61. Lähteenmäki, K.; Virkola, R.; Sarén, A.; Emödy, L.; Korhonen, T.K. Expression of plasminogen activator Pla of *Yersinia pestis* enhances bacterial attachment to the mammalian extracellular matrix. *Infect. Immun.* **1998**, *66*, 5755–5762. [[CrossRef](#)]
62. Lobo, L.A. Adhesive properties of the purified plasminogen activator Pla of *Yersinia pestis*. *FEMS Microbiol. Lett.* **2006**, *262*, 158–162. [[CrossRef](#)]
63. Cowan, C.; Jones, H.A.; Kaya, Y.H.; Perry, R.D.; Straley, S.C. Invasion of epithelial cells by *Yersinia pestis*: Evidence for a *Y. pestis*-specific invasin. *Infect. Immun.* **2000**, *68*, 4523–4530. [[CrossRef](#)]
64. Lähteenmäki, K.; Kukkonen, M.; Korhonen, T.K. The Pla surface protease/adhesin of *Yersinia pestis* mediates bacterial invasion into human endothelial cells. *FEBS Lett.* **2001**, *504*, 69–72. [[CrossRef](#)]
65. Fields, K.A.; Straley, S.C. LcrV of *Yersinia pestis* enters infected eukaryotic cells by a virulence plasmid-independent mechanism. *Infect. Immun.* **1999**, *67*, 4801–4813. [[CrossRef](#)] [[PubMed](#)]
66. Derewenda, U.; Mateja, A.; Devedjiev, Y.; Routzahn, K.M.; Evdokimov, A.G.; Derewenda, Z.S.; Waugh, D.S. The structure of *Yersinia pestis* V-antigen, an essential virulence factor and mediator of immunity against plague. *Structure* **2004**, *12*, 301–306. [[CrossRef](#)] [[PubMed](#)]
67. Price, S.B.; Cowan, C.; Perry, R.D.; Straley, S.C. The *Yersinia pestis* V antigen is a regulatory protein necessary for Ca<sup>2+</sup>(+)-dependent growth and maximal expression of low-Ca<sup>2+</sup> response virulence genes. *J. Bacteriol.* **1991**, *173*, 2649–2657. [[CrossRef](#)]
68. Hamad, M.A.; Nilles, M.L. Structure-function analysis of the C-terminal domain of LcrV from *Yersinia pestis*. *J. Bacteriol.* **2007**, *189*, 6734–6739. [[CrossRef](#)]
69. DiMezzo, T.L.; Ruthel, G.; Brueggemann, E.E.; Hines, H.B.; Ribot, W.J.; Chapman, C.E.; Powell, B.S.; Welkos, S.L. In vitro intracellular trafficking of virulence antigen during infection by *Yersinia pestis*. *PLoS ONE* **2009**, *4*, e6281. [[CrossRef](#)] [[PubMed](#)]
70. Sing, A.; Roggenkamp, A.; Geiger, A.M.; Heesemann, J. *Yersinia enterocolitica* evasion of the host innate immune response by V antigen-induced IL-10 production of macrophages is abrogated in IL-10-deficient mice. *J. Immunol.* **2002**, *168*, 1315–1321. [[CrossRef](#)] [[PubMed](#)]
71. Perry, R.D.; Haddix, P.; Atkins, E.B.; Soughers, T.K.; Straley, S.C. Regulation of expression of V antigen and outer membrane proteins in *Yersinia pestis*. *Contrib. Microbiol. Immunol.* **1987**, *9*, 173–178. [[PubMed](#)]

72. Perry, R.D.; Harmon, P.A.; Bowmer, W.S.; Straley, S.C. A low-Ca<sup>2+</sup> response operon encodes the V antigen of *Yersinia pestis*. *Infect. Immun.* **1986**, *54*, 428–434. [[CrossRef](#)] [[PubMed](#)]
73. Nilles, M.L.; Williams, A.W.; Skrzypek, E.; Straley, S.C. *Yersinia pestis* LcrV forms a stable complex with LcrG and may have a secretion-related regulatory role in the low-Ca<sup>2+</sup> response. *J. Bacteriol.* **1997**, *179*, 1307–1316. [[CrossRef](#)]
74. Fields, K.A.; Nilles, M.L.; Cowan, C.; Straley, S.C. Virulence role of V antigen of *Yersinia pestis* at the bacterial surface. *Infect. Immun.* **1999**, *67*, 5395–5408. [[CrossRef](#)] [[PubMed](#)]
75. Philipovskiy, A.V.; Cowan, C.; Wulff-Strobel, C.R.; Burnett, S.H.; Kerschen, E.J.; Cohen, D.A.; Kaplan, A.M.; Straley, S.C. Antibody against V antigen prevents Yop-dependent growth of *Yersinia pestis*. *Infect. Immun.* **2005**, *73*, 1532–1542. [[CrossRef](#)]
76. Nilles, M.L.; Fields, K.A.; Straley, S.C. The V antigen of *Yersinia pestis* regulates Yop vectorial targeting as well as Yop secretion through effects on YopB and LcrG. *J. Bacteriol.* **1998**, *180*, 3410–3420. [[CrossRef](#)]
77. Rosqvist, R.; Forsberg, A.; Rimpiläinen, M.; Bergman, T.; Wolf-Watz, H. The cytotoxic protein YopE of *Yersinia* obstructs the primary host defence. *Mol. Microbiol.* **1990**, *4*, 657–667. [[CrossRef](#)]
78. Bliska, J.B.; Black, D.S. Inhibition of the Fc receptor-mediated oxidative burst in macrophages by the *Yersinia pseudotuberculosis* tyrosine phosphatase. *Infect. Immun.* **1995**, *63*, 681–685. [[CrossRef](#)] [[PubMed](#)]
79. Fällman, M.; Andersson, K.; Håkansson, S.; Magnusson, K.E.; Stendahl, O.; Wolf-Watz, H. *Yersinia pseudotuberculosis* inhibits Fc receptor-mediated phagocytosis in J774 cells. *Infect. Immun.* **1995**, *63*, 3117–3124. [[CrossRef](#)]
80. Grosdent, N.; Maridonneau-Parini, I.; Paule Sory, M.; Cornelis, G.R. Role of Yops and adhesins in resistance of *Yersinia enterocolitica* to phagocytosis. *Infect. Immun.* **2002**, *70*, 4165–4176. [[CrossRef](#)]
81. Visser, L.G.; Annema, A.; van Furth, R. Role of Yops in inhibition of phagocytosis and killing of opsonized *Yersinia enterocolitica* by human granulocytes. *Infect. Immun.* **1995**, *63*, 2570–2575. [[CrossRef](#)]
82. Anderson, D.M.; Schneewind, O. *Yersinia enterocolitica* type III secretion: An mRNA signal that couples translation and secretion of YopQ. *Mol. Microbiol.* **1999**, *31*, 1139–1148. [[CrossRef](#)]
83. Heitzinger, K.; Impouma, B.; Farham, B.L.; Hambion, E.L.; Lukoya, C.; Machingaidze, C.; Rakotonjanabelo, L.A.; Yao, M.; Diallo, B.; Djingarey, M.H.; et al. Using evidence to inform response to the 2017 plague outbreak in Madagascar: A view from the WHO African Regional Office. *Epidemiol. Infect.* **2018**, *147*, 1–5. [[CrossRef](#)]
84. Nguyen, V.K.; Parra-Rojas, C.; Hernandez-Vargas, E.A. The 2017 plague outbreak in Madagascar: Data descriptions and epidemic modelling. *Epidemics* **2018**, *25*, 20–25. [[CrossRef](#)] [[PubMed](#)]
85. Vallès, X.; Stenseth, N.C.; Demeure, C.; Horby, P.; Mead, P.S.; Cabanillas, O.; Ratsitorahina, M.; Rajerison, M.; Andrianaivoarimanana, V.; Ramasindrazana, B.; et al. Human plague: An old scourge that needs new answers. *PLoS Negl. Trop. Dis.* **2020**, *14*, e0008251. [[CrossRef](#)]
86. Carniel, E. Plague today. *Med. Hist. Suppl.* **2008**, *52*, 115–122. [[CrossRef](#)]
87. Bertherat, E. Plague around the world, 2010–2015. *Wkly. Epidemiol. Rec.* **2016**, *91*, 89–93.
88. Bevins, S.N.; Baroch, J.A.; Nolte, D.L.; Zhang, M.; He, H. *Yersinia pestis*: Examining wildlife plague surveillance in China and the USA. *Integr. Zool.* **2012**, *7*, 99–109. [[CrossRef](#)] [[PubMed](#)]
89. Alderson, J.; Quastel, M.; Wilson, E.; Bellamy, D. Factors influencing the re-emergence of plague in Madagascar. *Emerg. Top. Life Sci.* **2020**, *4*, 411–421. [[PubMed](#)]
90. Randremanana, R.; Andrianaivoarimanana, V.; Nikolay, B.; Ramasindrazana, B.; Paireau, J.; Ten Bosch, Q.A.; Rakotondramanga, J.M.; Rahajandraibe, S.; Rahelinirina, S.; Rakotomanana, F.; et al. Epidemiological characteristics of an urban plague epidemic in Madagascar, August–November, 2017: An outbreak report. *Lancet Infect. Dis.* **2019**, *19*, 537–545. [[CrossRef](#)]
91. Andrianaivoarimanana, V.; Piola, P.; Wagner, D.M.; Rakotomanana, F.; Maheriniaina, V.; Andrianalimanana, S.; Chanteau, S.; Rahalison, L.; Ratsitorahina, M.; Rajerison, M. Trends of human plague, Madagascar, 1998–2016. *Emerg. Infect. Dis.* **2019**, *25*, 220–228. [[CrossRef](#)]
92. Rabaan, A.A.; Al-Ahmed, S.H.; Alsuliman, S.A.; Aldrazi, F.A.; Alfouzan, W.A.; Haque, S. The rise of pneumonic plague in Madagascar: Current plague outbreak breaks usual seasonal mould. *J. Med. Microbiol.* **2019**, *68*, 292–302. [[CrossRef](#)]
93. Barbieri, R.; Drancourt, M.; Raoult, D. The role of louse-transmitted diseases in historical plague pandemics. *Lancet Infect. Dis.* **2021**, *21*, e17–e25. [[CrossRef](#)]
94. WHO. *Madagascar Plague Outbreak: External Situation; Report #14*; WHO: Geneva, Switzerland, 2017.
95. Bragazzi, N.L.; Mahroum, N. Google trends predicts present and future plague cases during the plague outbreak in Madagascar: Infodemiological study. *JMIR Public Health Surveill* **2019**, *5*, e13142. [[CrossRef](#)]
96. Kilonzo, B.S.; Mvena, Z.S.; Machangu, R.S.; Mbise, T.J. Preliminary observations on factors responsible for long persistence and continued outbreaks of plague in Lushoto district, Tanzania. *Acta Trop.* **1997**, *68*, 215–227. [[CrossRef](#)]
97. Galimand, M.; Guiyoule, A.; Gerbaud, G.; Rasoamanana, B.; Chanteau, S.; Carniel, E.; Courvalin, P. Multidrug resistance in *Yersinia pestis* mediated by a transferable plasmid. *N. Engl. J. Med.* **1997**, *337*, 677–680. [[CrossRef](#)] [[PubMed](#)]
98. Godfred-Cato, S.; Cooley, K.M.; Fleck-Derderian, S.; Becksted, H.A.; Russell, Z.; Meaney-Delman, D.; Mead, P.S.; Nelson, C.A. Treatment of human plague: A systematic review of published aggregate data on antimicrobial efficacy, 1939–2019. *Clin. Infect. Dis.* **2020**, *70* (Suppl. S1), S11–S19. [[CrossRef](#)] [[PubMed](#)]
99. Kugeler, K.J.; Mead, P.S.; Campbell, S.B.; Nelson, C.A. Antimicrobial treatment patterns and illness outcome among United States patients with plague, 1942–2018. *Clin. Infect. Dis.* **2020**, *70* (Suppl. S1), S20–S26. [[CrossRef](#)] [[PubMed](#)]

100. Nelson, C.A.; Fleck-Derderian, S.; Cooley, K.M.; Meaney-Delman, D.; Becksted, H.A.; Russell, Z.; Renaud Bertherat, E.; Mead, P.S. Antimicrobial treatment of human plague: A systematic review of the literature on individual cases, 1937–2019. *Clin. Infect. Dis.* **2020**, *70* (Suppl. S1), S3–S10. [[CrossRef](#)]
101. Oyston, P.C.; Williamson, E.D. Prophylaxis and therapy of plague. *Expert Rev. Anti-Infect. Ther.* **2013**, *11*, 817–829. [[CrossRef](#)]
102. Dennis, D.T. Plague as a Biological Weapon. In *Bioterrorism and Infectious Agents: A New Dilemma for the 21st Century*; Fong, I.W., Alibek, K., Eds.; Springer New York: New York, NY, USA, 2009; pp. 37–70.
103. 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**, *55*, 3752–3757. [[CrossRef](#)]
104. Apangu, T.; Griffith, K.; Abaru, J.; Candini, G.; Apio, H.; Okoth, F.; Okello, R.; Kaggwa, J.; Acayo, S.; Ezama, G.; et al. Successful treatment of human plague with oral ciprofloxacin. *Emerg. Infect. Dis.* **2017**, *23*, 553–555. [[CrossRef](#)]
105. Welch, T.J.; Fricke, W.F.; McDermott, P.F.; White, D.G.; Rosso, M.L.; Rasko, D.A.; Mammel, M.K.; Eppinger, M.; Rosovitz, M.L.; Wagner, D.; et al. Multiple antimicrobial resistance in plague: An emerging public health risk. *PLoS ONE* **2007**, *2*, e309. [[CrossRef](#)]
106. Galimand, M.; Carniel, E.; Courvalin, P. Resistance of *Yersinia pestis* to antimicrobial agents. *Antimicrob. Agents Chemother.* **2006**, *50*, 3233–3236. [[CrossRef](#)]
107. Guiyoule, A.; Gerbaud, G.; Buchrieser, C.; Galimand, M.; Rahalison, L.; Chanteau, S.; Couvalin, P.; Carniel, E. Transferable plasmid-mediated resistance to streptomycin in a clinical isolate of *Yersinia pestis*. *Emerg. Infect. Dis.* **2001**, *7*, 43–48. [[CrossRef](#)]
108. Popowska, M.; Krawczyk-Balska, A. Broad-host-range IncP-1 plasmids and their resistance potential. *Front. Microbiol.* **2013**, *4*, 44. [[CrossRef](#)] [[PubMed](#)]
109. Cabanel, N.; Bouchier, C.; Rajerison, M.; Carniel, E. Plasmid-mediated doxycycline resistance in a *Yersinia pestis* strain isolated from a rat. *Int. J. Antimicrob. Agents* **2018**, *51*, 249–254. [[CrossRef](#)] [[PubMed](#)]
110. Dai, R.; He, J.; Zha, X.; Wang, Y.; Zhang, X.; Gao, H.; Yang, X.; Li, J.; Xin, Y.; Wang, Y.; et al. A novel mechanism of streptomycin resistance in *Yersinia pestis*: Mutation in the *rpsL* gene. *PLoS Negl. Trop. Dis.* **2021**, *15*, e0009324. [[CrossRef](#)] [[PubMed](#)]
111. Taitt, C.R.; Leski, T.A.; Chen, A.; Berk, K.L.; Dorsey, R.W.; Gregory, M.J.; Sozhamannan, S.; Frey, K.G.; Dutt, D.L.; Vora, G.J. A survey of antimicrobial resistance determinants in category a select agents, exempt strains, and near-neighbor species. *Int. J. Mol. Sci.* **2020**, *21*, 1669. [[CrossRef](#)] [[PubMed](#)]
112. Smiley, S.T. Current challenges in the development of vaccines for pneumonic plague. *Expert Rev. Vaccines* **2008**, *7*, 209–221. [[CrossRef](#)] [[PubMed](#)]
113. Titball, R.W.; Williamson, E.D. Vaccination against bubonic and pneumonic plague. *Vaccine* **2001**, *19*, 4175–4184. [[CrossRef](#)]
114. Sun, W.; Singh, A.K. Plague vaccine: Recent progress and prospects. *NPJ Vaccines* **2019**, *4*, 11. [[CrossRef](#)] [[PubMed](#)]
115. Cavanaugh, D.C. K.F. Meyer's work on plague. *J. Infect. Dis.* **1974**, *129* (Suppl. S1), S10–S12. [[CrossRef](#)]
116. Meyer, K.F.; Smith, G.; Foster, L.E.; Marshall, J.D., Jr.; Cavanaugh, D.C. Plague immunization. IV. Clinical reactions and serologic response to inoculations of Haffkine and freeze-dried plague vaccine. *J. Infect. Dis.* **1974**, *129*, S30–S36. [[CrossRef](#)]
117. Bartelloni, P.J.; Marshall, J.D., Jr.; Cavanaugh, D.C. Clinical and serological responses to plague vaccine U.S.P. *Mil. Med.* **1973**, *138*, 720–722. [[CrossRef](#)]
118. Cavanaugh, D.C.; Elisberg, B.L.; Llewellyn, C.H.; Marshall, J.D., Jr.; Rust, J.H., Jr.; Williams, J.E.; Meyer, K.F. Plague immunization. V. Indirect evidence for the efficacy of plague vaccine. *J. Infect. Dis.* **1974**, *129* (Suppl. S1), S37–S40. [[CrossRef](#)]
119. Meyer, K.F.; Smith, G.; Foster, L.; Brookman, M.; Sung, M. Live, attenuated *Yersinia pestis* vaccine: Virulent in nonhuman primates, harmless to guinea pigs. *J. Infect. Dis.* **1974**, *129*, S85–S112. [[CrossRef](#)]
120. Titball, R.W.; Williamson, E.D. *Yersinia pestis* (plague) vaccines. *Expert Opin. Biol. Ther.* **2004**, *4*, 965–973. [[CrossRef](#)]
121. Marshall, J.D., Jr.; Bartelloni, P.J.; Cavanaugh, D.C.; Kadull, P.J.; Meyer, K.F. Plague immunization. II. Relation of adverse clinical reactions to multiple immunizations with killed vaccine. *J. Infect. Dis.* **1974**, *129*, S19–S25. [[CrossRef](#)]
122. Russell, P.; Eley, S.M.; Hibbs, S.E.; Manchee, R.J.; Stagg, A.J.; Titball, R.W. A comparison of Plague vaccine, USP and EV76 vaccine induced protection against *Yersinia pestis* in a murine model. *Vaccine* **1995**, *13*, 1551–1556. [[CrossRef](#)]
123. Andrews, G.P.; Health, D.G.; Anderson, G.W.; Welkos, S.L.; Friedlander, A.M. Fraction 1 capsular antigen (F1) purification from *Yersinia pestis* CO92 and from an *Escherichia coli* recombinant strain and efficacy against lethal plague challenge. *Infect. Immun.* **1996**, *64*, 2180–2187. [[CrossRef](#)] [[PubMed](#)]
124. Smith, H.; Packman, L.P. A filtered non-toxic plague vaccine which protects guinea-pigs and mice. *Br. J. Exp. Pathol.* **1966**, *47*, 25–34. [[PubMed](#)]
125. Pitt, L.M. Non-human primates as a model for pneumonic plague: Animal models and correlates of protection for plague. In Proceedings of the Plague Vaccines Workshop, Gaithersburg, MD, USA, 13–14 October 2004.
126. Branger, C.G.; Torres-Escobar, A.; Sun, W.; Perry, R.; Fetherston, J.D.; Roland, K.; Curtiss, R. Oral vaccination with LcrV from *Yersinia pestis* KIM delivered by live attenuated *Salmonella enterica* serovar Typhimurium elicits a protective immune response against challenge with *Yersinia pseudotuberculosis* and *Yersinia enterocolitica*. *Vaccine* **2009**, *27*, 5363–5370. [[CrossRef](#)] [[PubMed](#)]
127. Branger, C.G.; Sun, W.; Torres-Escobar, A.; Perry, R.; Roland, K.L.; Fetherston, J.; Curtiss, R. Evaluation of Psn, HmuR and a modified LcrV protein delivered to mice by live attenuated *Salmonella* as a vaccine against bubonic and pneumonic *Yersinia pestis* challenge. *Vaccine* **2010**, *29*, 274–282. [[CrossRef](#)]
128. Branger, C.G.; Fetherston, J.D.; Perry, R.D.; Curtiss, R. Oral vaccination with different antigens from *Yersinia pestis* KIM delivered by live attenuated *Salmonella typhimurium* elicits a protective immune response against plague. *Adv. Exp. Med. Biol.* **2007**, *603*, 387–399.

129. Girard, G.; Robic, J. Current status of the plague in Madagascar and vaccinal prophylaxis with the aid of the EV virus-vaccine. *Bull. Soc. Path. Exot.* **1942**, *35*, 43–49.
130. Feodorov, V.A.; Lyapina, A.M.; Ulianova, O.V.; Lyapina, E.P.; Sayapina, L.V.; Lyapin, M.N.; Shcherbakov, A.A.; Telepnev, M.V.; Motin, V.L. Serologic markers for long-term immunity in humans vaccinated with live *Yersinia pestis* EV NIIEG. *Procedia Vaccinol.* **2012**, *6*, 10–13. [[CrossRef](#)]
131. Meyer, K.F.; Cavanaugh, D.C.; Bartelloni, P.J.; Marshall, J.D., Jr. Plague immunization. I. Past and present trends. *J. Infect. Dis.* **1974**, *129*, S13–S18. [[CrossRef](#)]
132. Feodorova, V.A.; Sayapina, L.V.; Corbel, M.J.; Motin, V.L. Russian vaccines against especially dangerous bacterial pathogens. *Emerg. Microbes Infect.* **2014**, *3*, e86. [[CrossRef](#)] [[PubMed](#)]
133. Wang, X.; Zhang, X.; Zhou, D.; Yang, R. Live-attenuated *Yersinia pestis* vaccines. *Expert Rev. Vaccines* **2013**, *12*, 677–686. [[CrossRef](#)]
134. Sun, W.; Roland, K.L.; Curtiss, R. Developing live vaccines against plague. *J. Infect. Dev. Ctries.* **2011**, *5*, 614–627. [[CrossRef](#)] [[PubMed](#)]
135. Sun, W.; Curtiss, R. Rational considerations about development of live attenuated *Yersinia pestis* vaccines. *Curr. Pharm. Biotechnol.* **2013**, *14*, 878–886. [[CrossRef](#)] [[PubMed](#)]
136. Bubeck, S.S.; Dube, P.H. *Yersinia pestis* CO92 delta *yopH* is a potent live, attenuated plague vaccine. *Clin. Vaccine Immunol.* **2007**, *14*, 1235–1238. [[CrossRef](#)] [[PubMed](#)]
137. Bozue, J.; Cote, C.K.; Webster, W.; Bassett, A.; Tobery, S.; Little, S.; Swietnicki, W. A *Yersinia pestis* YscN ATPase mutant functions as a live attenuated vaccine against bubonic plague in mice. *FEMS Microbiol. Lett.* **2012**, *332*, 113–121. [[CrossRef](#)]
138. Culbreth, M.J.; Biryukov, S.S.; Shoe, J.L.; Dankmeyer, J.L.; Hunter, M.; Klimko, C.P.; Rosario-Acevedo, R.; Fetterer, D.P.; Moreau, A.M.; Welkos, S.L.; et al. The use of analgesics during vaccination with a live attenuated *Yersinia pestis* vaccine alters the resulting immune response in mice. *Vaccines* **2019**, *7*, 205. [[CrossRef](#)] [[PubMed](#)]
139. Cote, C.K.; Biryukov, S.S.; Klimko, C.P.; Shoe, J.L.; Hunter, M.; Rosario-Acevedo, R.; Fetterer, D.P.; Moody, K.L.; Meyer, J.R.; Rill, N.O.; et al. Protection elicited by attenuated Live *Yersinia pestis* vaccine strains against lethal infection with virulent, *Y. pestis*. *Vaccines* **2021**, *9*, 161. [[CrossRef](#)]
140. Jenkins, A.L.; Worsham, P.L.; Welkos, S.L. A strategy to verify the absence of the *pgm* locus in *Yersinia pestis* strain candidates for select agent exemption. *J. Microbiol. Methods* **2009**, *77*, 316–319. [[CrossRef](#)]
141. Welkos, S.; Pitt, M.L.; Martinez, M.; Friedlander, A.; Vogel, P.; Tammariello, R. Determination of the virulence of the pigmentation-deficient and pigmentation-/plasminogen activator-deficient strains of *Yersinia pestis* in non-human primate and mouse models of pneumonic plague. *Vaccine* **2002**, *20*, 2206–2214. [[CrossRef](#)]
142. Demeure, C.E.; Derbise, A.; Carniel, E. Oral vaccination against plague using *Yersinia pseudotuberculosis*. *Chem. Biol. Interact.* **2017**, *267*, 89–95. [[CrossRef](#)] [[PubMed](#)]
143. Singh, A.K.; Curtiss, R., 3rd; Sun, W. A recombinant attenuated *Yersinia pseudotuberculosis* vaccine delivering a *Y. pestis* YopE(Nt138)-LcrV fusion elicits broad protection against plague and yersiniosis in mice. *Infect. Immun.* **2019**, *87*, e00296–19. [[CrossRef](#)] [[PubMed](#)]
144. Sun, W.; Sanapala, S.; Rahav, H.; Curtiss, R., 3rd. Oral administration of a recombinant attenuated *Yersinia pseudotuberculosis* strain elicits protective immunity against plague. *Vaccine* **2015**, *33*, 6727–6735. [[CrossRef](#)] [[PubMed](#)]
145. Sun, W.; Sanapala, S.; Henderson, J.C.; Sam, S.; Olinzock, J.; Trent, M.S.; Curtiss, R., 3rd. LcrV delivered via type III secretion system of live attenuated *Yersinia pseudotuberculosis* enhances immunogenicity against pneumonic plague. *Infect. Immun.* **2014**, *82*, 4390–4404. [[CrossRef](#)]
146. Hervé, C.; Laupèze, B.; Del Giudice, G.; Didierlaurent, A.M.; Tavares Da Silva, F. The how's and what's of vaccine reactogenicity. *NPJ Vaccines* **2019**, *4*, 39. [[CrossRef](#)]
147. Williamson, E.D.; Eley, S.M.; Stagg, A.J.; Green, M.; Russell, P.; Titball, R.W. A sub-unit vaccine elicits IgG in serum, spleen cell cultures and bronchial washings and protects immunized animals against pneumonic plague. *Vaccine* **1997**, *15*, 1079–1084. [[CrossRef](#)]
148. Jones, S.M.; Day, F.; Stagg, A.J.; Williamson, E.D. Protection conferred by a fully recombinant sub-unit vaccine against *Yersinia pestis* in male and female mice of four inbred strains. *Vaccine* **2000**, *19*, 358–366. [[CrossRef](#)]
149. Al-Jawdah, A.D.; Ivanova, I.G.; Waller, H.; Perkins, N.D.; Lakey, J.H.; Peters, D.T. Induction of the immunoprotective coat of *Yersinia pestis* at body temperature is mediated by the Caf1R transcription factor. *BMC Microbiol.* **2019**, *19*, 68. [[CrossRef](#)]
150. Galyov, E.E.; Smirnov, O.Y.; Karlishchev, A.V.; Volkovoy, K.I.; Denesyuk, A.I.; Nazimov, I.V.; Rubtsov, K.S.; Abramov, V.M.; Dalvadyanz, S.M.; Zavyalov, V.P. Nucleotide sequence of the *Yersinia pestis* gene encoding F1 antigen and the primary structure of the protein. *FEBS Lett.* **1990**, *277*, 230–232. [[CrossRef](#)]
151. Karlyshev, A.V.; Galyov, E.E.; Smirnov, O.Y.; Guzayev, A.P.; Abramov, V.M.; Zavyalov, V.P. A new gene of the *f1* operon of *Y. pestis* involved in the capsule biogenesis. *FEBS Lett.* **1992**, *297*, 77–80. [[CrossRef](#)]
152. Donavan, J.E.; Ham, D.; Fukui, G.M.; Sargalla, M.J. Role of the capsule of *Pasteurella Pestis* in bubonic plague in the guinea pig. *J. Infect. Dis.* **1961**, *109*, 154–157. [[CrossRef](#)] [[PubMed](#)]
153. Vorontsov, E.D.; Dubichev, A.G.; Serdobintsev, L.N.; Naumov, A.V. Association-dissociation processes and supermolecular organisation of the capsule antigen (protein F1) of *Yersinia pestis*. *Biomed. Sci.* **1990**, *1*, 391–396. [[PubMed](#)]
154. Burrows, T.W.; Bacon, G.A. The effects of loss of different virulence determinants on the virulence and immunogenicity of strains of *Pasteurella pestis*. *Br. J. Exp. Pathol.* **1958**, *39*, 278–291. [[PubMed](#)]

155. Anderson, G.W., Jr.; Leary, S.E.; Williamson, E.D.; Titball, R.; Welkos, S.L.; Wosham, P.L.; Friendlander, A.M. Recombinant V antigen protects mice against pneumonic and bubonic plague caused by F1-capsule-positive and -negative strains of *Yersinia pestis*. *Infect. Immun.* **1996**, *64*, 4580–4585. [[CrossRef](#)]
156. Hill, J.; Leary, S.E.; Griffin, K.F.; Williamson, E.D.; Titball, R.W. Regions of *Yersinia pestis* V antigen that contribute to protection against plague identified by passive and active immunization. *Infect. Immun.* **1997**, *65*, 4476–4482. [[CrossRef](#)]
157. Leary, S.E.; Williamson, E.D.; Griffin, K.F.; Russell, P.; Eley, R.W.; Titball, R.W. Active immunization with recombinant V antigen from *Yersinia pestis* protects mice against plague. *Infect. Immun.* **1995**, *63*, 2854–2858. [[CrossRef](#)]
158. Weeks, S.; Hill, J.; Friendlander, A.; Welkos, S. Anti-V antigen antibody protects macrophages from *Yersinia pestis* -induced cell death and promotes phagocytosis. *Microb. Pathog.* **2002**, *32*, 227–237. [[CrossRef](#)]
159. Pettersson, J.; Holmström, A.; Hill, J.; Leary, S.; Frithz-Lindsten, E.; von Euler-Matell, A.; Carlsson, E.; Titball, R.; Forsberg, A.; Wolf-Watz, H. The V-antigen of *Yersinia* is surface exposed before target cell contact and involved in virulence protein translocation. *Mol. Microbiol.* **1999**, *32*, 961–976. [[CrossRef](#)]
160. Sawa, T.; Yahr, T.L.; Ohara, M.; Kurahashi, K.; Gropper, M.A.; Wiener-Kronish, J.P.; Frank, D.W. Active and passive immunization with the *Pseudomonas* V antigen protects against type III intoxication and lung injury. *Nat. Med.* **1999**, *5*, 392–398. [[CrossRef](#)]
161. Anisimov, A.P.; Dentovskaya, A.V.; Panfertsev, E.A.; Svetoch, T.E.; Kopylov, P.K.; Segelke, B.W.; Zemla, A.; Telepnev, M.V.; Motin, V.L. Amino acid and structural variability of *Yersinia pestis* LcrV protein. *Infect. Genet. Evol.* **2010**, *10*, 137–145. [[CrossRef](#)] [[PubMed](#)]
162. Simpson, W.J.; Thomas, R.E.; Schwan, T.G. Recombinant capsular antigen (fraction 1) from *Yersinia pestis* induces a protective antibody response in BALB/c mice. *Am. J. Trop. Med. Hyg.* **1990**, *43*, 389–396. [[CrossRef](#)] [[PubMed](#)]
163. Carr, S.; Miller, J.; Leary, S.E.; Bennett, A.M.; Ho, A.; Williamson, E.D. Expression of a recombinant form of the V antigen of *Yersinia pestis*, using three different expression systems. *Vaccine* **1999**, *18*, 153–159. [[CrossRef](#)]
164. Chichester, J.A.; Musychuk, K.; Farrance, C.E.; Mett, V.; Lyons, J.; Mett, V.; Yusibov, V. A single component two-valent LcrV-F1 vaccine protects non-human primates against pneumonic plague. *Vaccine* **2009**, *27*, 3471–3474. [[CrossRef](#)] [[PubMed](#)]
165. Williamson, E.D.; Vesey, P.M.; Gillhespy, K.J.; Eley, S.M.; Green, M.; Titball, R.W. An IgG1 titre to the F1 and V antigens correlates with protection against plague in the mouse model. *Clin. Exp. Immunol.* **1999**, *116*, 107–114. [[CrossRef](#)]
166. Powell, B.S.; Andrews, G.P.; Enama, J.T.; Jenderk, S.; Bolt, C.; Worsham, P.; Pullen, J.K.; Ribot, W.; Hines, H.; Smith, L.; et al. Design and testing for a nontagged F1-V fusion protein as vaccine antigen against bubonic and pneumonic plague. *Biotechnol. Prog.* **2005**, *21*, 1490–1510. [[CrossRef](#)]
167. Goodin, J.L.; Nellis, D.F.; Powell, B.S.; Vyas, V.V.; Enama, J.T.; Wang, L.C.; Clark, P.K.; Giardina, S.L.; Adamovicz, J.J.; Michiel, D.F. Purification and protective efficacy of monomeric and modified *Yersinia pestis* capsular F1-V antigen fusion proteins for vaccination against plague. *Protein Exp. Purif.* **2007**, *53*, 63–79. [[CrossRef](#)]
168. Fellows, P.; Adamovicz, J.; Hartings, J.; Sherwood, R.; Mega, W.; Brasel, T.; Barr, E.; Holland, L.; Lin, W.; Rom, A.; et al. Protection in mice passively immunized with serum from cynomolgus macaques and humans vaccinated with recombinant plague vaccine (rF1V). *Vaccine* **2010**, *28*, 7748–7756. [[CrossRef](#)]
169. Glynn, A.; Roy, C.J.; Powell, B.S.; Adamovicz, J.J.; Freytag, L.C.; Clements, J.D. Protection against aerosolized *Yersinia pestis* challenge following homologous and heterologous prime-boost with recombinant plague antigens. *Infect. Immun.* **2005**, *73*, 5256–5261. [[CrossRef](#)]
170. Heath, D.G.; Anderson, G.W.; Mauro, J.M.; Welkos, S.L.; Andrews, G.P.; Adamovicz, J.; Friedlander, A.M. Protection against experimental bubonic and pneumonic plague by a recombinant capsular F1-V antigen fusion protein vaccine. *Vaccine* **1998**, *16*, 1131–1137. [[CrossRef](#)]
171. Williamson, E.D.; Eley, S.M.; Stagg, A.J.; Green, M.; Russell, P.; Titball, R.W. A single dose sub-unit vaccine protects against pneumonic plague. *Vaccine* **2000**, *19*, 566–571. [[CrossRef](#)]
172. Williamson, E.D.; Eley, S.M.; Griffin, K.F.; Green, M.; Russell, P.; Leary, S.E.; Oyston, P.C.; Easterbrokk, T.; Reddin, K.M.; Robinson, A. A new improved sub-unit vaccine for plague: The basis of protection. *FEMS Immunol. Med. Microbiol.* **1995**, *12*, 223–230. [[CrossRef](#)] [[PubMed](#)]
173. Elvin, S.J.; Williamson, E.D. The F1 and V subunit vaccine protects against plague in the absence of IL-4 driven immune responses. *Microb. Pathog.* **2000**, *29*, 223–230. [[CrossRef](#)]
174. Sun, W. Plague Vaccines: Status and Future. *Adv. Exp. Med. Biol.* **2016**, *918*, 313–360.
175. Quenee, L.E.; Schneewind, O. Plague vaccines and the molecular basis of immunity against *Yersinia pestis*. *Hum. Vaccine* **2009**, *5*, 817–823. [[CrossRef](#)]
176. Quenee, L.E.; Ciletti, N.A.; Elli, D.; Hermanas, T.M.; Schneewind, O. Prevention of pneumonic plague in mice, rats, guinea pigs and non-human primates with clinical grade rV10, rV10-2 or F1-V vaccines. *Vaccine* **2011**, *29*, 6572–6583. [[CrossRef](#)]
177. Williamson, E.D.; Packer, P.J.; Waters, E.L.; Simpson, D.D.; Hartings, J.; Twenhafel, N.; Pitt, M.L. Recombinant (F1+V) vaccine protects cynomolgus macaques against pneumonic plague. *Vaccine* **2011**, *29*, 4771–4777. [[CrossRef](#)]
178. Amemiya, K.; Meyers, J.L.; Rogers, T.E.; Fast, R.L.; Bassett, A.D.; Worsham, P.L.; Powell, B.S.; Norris, S.L.; Krieg, A.M.; Adamovicz, J.J. CpG oligodeoxynucleotides augment the murine immune response to the *Yersinia pestis* F1-V vaccine in bubonic and pneumonic models of plague. *Vaccine* **2009**, *27*, 2220–2229. [[CrossRef](#)]
179. D’Arco, C.; McCormick, A.A.; Arnaboldi, P.M. Single-dose intranasal subunit vaccine rapidly clears secondary sepsis in a high-dose pneumonic plague infection. *Vaccine* **2021**, *39*, 1435–1444. [[CrossRef](#)]



180. Kilgore, P.B.; Sha, J.; Anderson, J.A.; Motin, V.L.; Chopra, A.K. A new generation needle- and adjuvant-free trivalent plague vaccine utilizing adenovirus-5 nanoparticle platform. *NPJ Vaccines* **2021**, *6*, 21. [[CrossRef](#)] [[PubMed](#)]
181. Hamzabegovic, F.; Goll, J.B.; Hooper, W.F.; Frey, S.; Gelber, C.E.; Abate, G. Flagellin adjuvanted F1/V subunit plague vaccine induces T cell and functional antibody responses with unique gene signatures. *NPJ Vaccines* **2020**, *5*, 6. [[CrossRef](#)] [[PubMed](#)]
182. Del Prete, G.; Santi, L.; Andrianaivoarimanana, V.; Amedei, A.; Domarle, O.; D'Elia, M.M.; Arntzen, C.J.; Rahalison, L.; Mason, H.S. Plant-derived recombinant F1, V, and F1-V fusion antigens of *Yersinia pestis* activate human cells of the innate and adaptive immune system. *Int. J. Immunopathol. Pharmacol.* **2009**, *22*, 133–143. [[CrossRef](#)]
183. Jones, T.; Adamovicz, J.J.; Cyr, S.L.; Bolt, C.R.; Bellerose, N.; Pitt, L.M.; Lowell, G.H.; Burt, D.S. Intranasal Protollin/F1-V vaccine elicits respiratory and serum antibody responses and protects mice against lethal aerosolized plague infection. *Vaccine* **2006**, *24*, 1625–1632. [[CrossRef](#)] [[PubMed](#)]
184. Goodin, J.L.; Powell, B.S.; Enama, J.T.; Raab, R.W.; McKown, R.L.; Coffman, G.L.; Andrews, G.P. Purification and characterization of a recombinant *Yersinia pestis* V-F1 “Reversed” fusion protein for use as a new subunit vaccine against plague. *Protein Exp. Purif.* **2011**, *76*, 136–144. [[CrossRef](#)]
185. Yamanaka, H.; Hoyt, T.; Yang, X.; Golden, S.; Bosio, C.M.; Crist, K.; Becker, T.; Maddaloni, M.; Pascual, D.W. A nasal interleukin-12 DNA vaccine coexpressing *Yersinia pestis* F1-V fusion protein confers protection against pneumonic plague. *Infect. Immun.* **2008**, *76*, 4564–4573. [[CrossRef](#)]
186. Jones, S.; Griffin, K.; Hodgson, I.; Williamson, E. Protective efficacy of a fully recombinant plague vaccine in the guinea pig. *Vaccine* **2003**, *21*, 3912–3918. [[CrossRef](#)]
187. Williamson, E.D.; Flick-Smith, H.C.; Lebitt, C.; Rowland, C.A.; Jones, S.M.; Waters, E.L.; Gwyther, R.J.; Miller, J.; Packer, P.J.; Irving, M. Human immune response to a plague vaccine comprising recombinant F1 and V antigens. *Infect. Immun.* **2005**, *73*, 3598–3608. [[CrossRef](#)]
188. Andrews, G.P.; Strachan, S.T.; Benner, G.E.; Sample, A.K.; Anderson, G.W., Jr.; Adamovicz, J.J.; Welkos, S.L.; Pullen, J.K.; Friedlander, A.M. Protective efficacy of recombinant *Yersinia* outer proteins against bubonic plague caused by encapsulated and nonencapsulated *Yersinia pestis*. *Infect. Immun.* **1999**, *67*, 1533–1537. [[CrossRef](#)]
189. Ivanov, M.I.; Noel, B.L.; Rampersaud, R.; Mena, P.; Benach, J.L.; Bliska, J.B. Vaccination of mice with a Yop translocon complex elicits antibodies that are protective against infection with F1- *Yersinia pestis*. *Infect. Immun.* **2008**, *76*, 5181–5190. [[CrossRef](#)]
190. Motin, V.L.; Nakajima, R.; Smirnov, G.B.; Brubaker, R.R. Passive immunity to yersiniae mediated by anti-recombinant V antigen and protein A-V antigen fusion peptide. *Infect. Immun.* **1994**, *62*, 4192–4201. [[CrossRef](#)]
191. Quenee, L.E.; Berube, B.J.; Segal, J.; Elli, D.; Ciletti, N.A.; Anderson, D.; Schneewind, O. Amino acid residues 196–226 of LcrV represent a plague protective epitope. *Vaccine* **2010**, *28*, 1870–1876. [[CrossRef](#)] [[PubMed](#)]
192. Amemiya, K.; Dankmeyer, J.L.; Keasey, S.L.; Trevino, S.R.; Wormald, M.M.; Halasohoris, S.A.; Ribot, W.J.; Fetterer, D.P.; Cote, C.K.; Worsham, P.L.; et al. Binding sites of anti-LcrV monoclonal antibodies are more critical than the avidities and affinities for passive protection against *Yersinia pestis* infection in a bubonic plague model. *Antibodies* **2020**, *9*, 37. [[CrossRef](#)] [[PubMed](#)]
193. Cowan, C.; Philipovskiy, A.V.; Wulff-Strobel, C.R.; Ye, Z.; Straley, S.C. Anti-LcrV antibody inhibits delivery of Yops by *Yersinia pestis* KIM5 by directly promoting phagocytosis. *Infect. Immun.* **2005**, *73*, 6127–6137. [[CrossRef](#)] [[PubMed](#)]
194. Eisele, N.A.; Anderson, D.M. Dual-function antibodies to *Yersinia pestis* LcrV required for pulmonary clearance of plague. *Clin. Vaccine Immunol.* **2009**, *16*, 1720–1727. [[CrossRef](#)] [[PubMed](#)]
195. Sofer-Podesta, C.; Ang, J.; Hackett, N.R.; Senina, S.; Perlin, D.; Crystal, R.G.; Boyer, J.L. Adenovirus-mediated delivery of an anti-V antigen monoclonal antibody protects mice against a lethal *Yersinia pestis* challenge. *Infect. Immun.* **2009**, *77*, 1561–1568. [[CrossRef](#)]
196. Miller, N.C.; Quenee, L.E.; Elli, D.; Ciletti, N.A.; Schneewind, O. Polymorphisms in the *lcrV* gene of *Yersinia enterocolitica* and their effect on plague protective immunity. *Infect. Immun.* **2012**, *80*, 1572–1582. [[CrossRef](#)] [[PubMed](#)]
197. Roggenkamp, A.; Geiger, A.M.; Leitritz, L.; Kessler, A.; Heesemann, J. Passive immunity to infection with *Yersinia* spp. mediated by anti-recombinant V antigen is dependent on polymorphism of V antigen. *Infect. Immun.* **1997**, *65*, 446–451. [[CrossRef](#)]
198. Daniel, C.; Dewitte, A.; Poirer, S.; Marceau, M.; Simonet, M.; Marceau, L.; Descombes, G.; Boutillier, D.; Bennaceur, N.; Bontemps-Gallo, S.; et al. Polymorphism in the yersinia LcrV antigen enables immune escape from the protection conferred by an LcrV-secreting *Lactococcus lactis* in a pseudotuberculosis mouse model. *Front. Immunol.* **2019**, *10*, 1830. [[CrossRef](#)]
199. Anderson, G.W., Jr.; Worsham, P.L.; Bolt, C.R.; Andrews, G.P.; Welkos, S.L.; Friedlander, A.M. Protection of mice from fatal bubonic and pneumonic plague by passive immunization with monoclonal antibodies against the F1 protein of *Yersinia pestis*. *Am. J. Trop. Med. Hyg.* **1997**, *56*, 471–473. [[CrossRef](#)]
200. Hill, J.; Copse, C.; Leary, S.; Stagg, A.J.; Williamson, E.D.; Titball, R.W. Synergistic protection of mice against plague with monoclonal antibodies specific for the F1 and V antigens of *Yersinia pestis*. *Infect. Immun.* **2003**, *71*, 2234–2238. [[CrossRef](#)]
201. Hill, J.; Eyles, J.E.; Elvin, S.J.; Healey, G.D.; Lukaszewski, R.A.; Titball, R.W. Administration of antibody to the lung protects mice against pneumonic plague. *Infect. Immun.* **2006**, *74*, 3068–3070. [[CrossRef](#)]
202. Xiao, X.; Zhu, Z.; Dankmeyer, J.L.; Wormald, M.M.; Fast, R.L.; Worsham, P.L.; Cote, C.K.; Amemiya, K.; Dimitrov, D.S. Human anti-plague monoclonal antibodies protect mice from *Yersinia pestis* in a bubonic plague model. *PLoS ONE* **2010**, *5*, e13047. [[CrossRef](#)]

203. Liu, W.; Ren, J.; Zhang, J.; Song, X.; Lui, S.; Chi, X.; Chen, Y.; Wem, Z.; Li, J.; Chen, W. Identification and characterization of a neutralizing monoclonal antibody that provides complete protection against *Yersinia pestis*. *PLoS ONE* **2017**, *12*, e0177012. [[CrossRef](#)]
204. Lillo, A.M.; Velappan, N.; Kelliher, J.M.; Watts, A.J.; Merriman, S.P.; Vuyisich, G.; Lilley, L.M.; Coombs, K.E.; Mastren, T.; Teshima, M.; et al. Development of anti-*Yersinia pestis* human antibodies with features required for diagnostic and therapeutic applications. *Immunotargets Ther.* **2020**, *9*, 299–316. [[CrossRef](#)] [[PubMed](#)]
205. Navalkele, B.D.; Chopra, T. Bezlotoxumab: An emerging monoclonal antibody therapy for prevention of recurrent *Clostridium difficile* infection. *Biologics* **2018**, *12*, 11–21. [[CrossRef](#)] [[PubMed](#)]
206. Humphreys, D.P.; Wilcox, M.H. Antibodies for treatment of *Clostridium difficile* infection. *Clin. Vaccine Immunol.* **2014**, *21*, 913–923. [[CrossRef](#)]
207. Chen, Z.; Moayeri, M.; Purcell, R. Monoclonal antibody therapies against anthrax. *Toxins* **2011**, *3*, 1004–1019. [[CrossRef](#)]
208. Pelfrene, E.; Mura, M.; Cavaleiro Sanches, A.; Cavaleri, M. Monoclonal antibodies as anti-infective products: A promising future? *Clin. Microbiol. Infect.* **2019**, *25*, 60–64. [[CrossRef](#)] [[PubMed](#)]
209. Schweizer, H.P. Mechanisms of antibiotic resistance in *Burkholderia pseudomallei*: Implications for treatment of melioidosis. *Future Microbiol.* **2012**, *7*, 1389–1399. [[CrossRef](#)] [[PubMed](#)]
210. Jarrad, A.M.; Karoli, T.; Blaskovich, M.A.; Lyras, D.; Cooper, M.A. *Clostridium difficile* drug pipeline: Challenges in discovery and development of new agents. *J. Med. Chem.* **2015**, *58*, 5164–5185. [[CrossRef](#)] [[PubMed](#)]
211. Merriman, H. Chapter 13—Infectious diseases. In *Acute Care Handbook for Physical Therapists*, 4th ed.; Paz, J.C., West, M.P., Eds.; W.B. Saunders: St. Louis, MO, USA, 2014; pp. 313–334.
212. Santajit, S.; Indrawattana, N. Mechanisms of antimicrobial resistance in ESKAPE pathogens. *Biomed. Res. Int.* **2016**, *2016*, 2475067. [[CrossRef](#)] [[PubMed](#)]
213. Pachori, P.; Gothwal, R.; Gandhi, P. Emergence of antibiotic resistance *Pseudomonas aeruginosa* in intensive care unit; a critical review. *Genes Dis.* **2019**, *6*, 109–119. [[CrossRef](#)] [[PubMed](#)]
214. González-González, E.; Alvarez, M.M.; Márquez-Ipiña, A.R.; Trujillo-de Santiago, G.; Rodríguez-Martínez, L.M.; Annabi, N.; Khademhosseini, A. Anti-Ebola therapies based on monoclonal antibodies: Current state and challenges ahead. *Crit. Rev. Biotechnol.* **2017**, *37*, 53–68. [[CrossRef](#)]
215. Bailey, M.J.; Broecker, F.; Freyn, A.W.; Choi, A.; Brown, J.A.; Federova, N.; Simon, V.; Lim, J.K.; Evans, M.J.; García-Sastre, A.; et al. Human monoclonal antibodies potently neutralize Zika virus and select for escape mutations on the lateral ridge of the envelope protein. *J. Virol.* **2019**, *93*, e00405–19. [[CrossRef](#)]
216. Marovich, M.; Mascola, J.R.; Cohen, M.S. Monoclonal antibodies for prevention and treatment of COVID-19. *JAMA* **2020**, *324*, 131–132. [[CrossRef](#)] [[PubMed](#)]
217. Jahanshahlu, L.; Rezaei, N. Monoclonal antibody as a potential anti-COVID-19. *Biomed. Pharmacother.* **2020**, *129*, 110337. [[CrossRef](#)]
218. Lülfi, S.; Matz, J.; Rouyez, M.C.; Järviuoma, A.; Saksela, K.; Benichou, S.; Geyer, M. Structural basis for the inhibition of HIV-1 Nef by a high-affinity binding single-domain antibody. *Retrovirology* **2014**, *11*, 24. [[CrossRef](#)]
219. Cruz-Teran, C.; Tiruthani, K.; McSweeney, M.; Ma, A.; Pickles, R.; Lai, S.K. Challenges and opportunities for antiviral monoclonal antibodies as COVID-19 therapy. *Adv. Drug Deliv. Rev.* **2021**, *169*, 100–117. [[CrossRef](#)] [[PubMed](#)]
220. Pecetta, S.; Finco, O.; Seubert, A. Quantum leap of monoclonal antibody (mAb) discovery and development in the COVID-19 era. *Semin. Immunol.* **2020**, *50*, 101427. [[CrossRef](#)]