

Plague Vaccine Modern Progress and Prospects

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Abstract: Three great pandemics, resulting in nearly 200 million deaths in human history and usage made Bio warfare agent, have made *Yersinia pestis* as one of the most virulent human pathogens. prophylactic vaccination counter acting this disease is Certainly a primary choice for its long term prevention in late 2017, a large plague outbreak rag review Madagascar attracted extensive attention and caused regional panics. Inhalation of *Yersinia-pestis* bacilli causes pneumonic plague a fast growing and deadly dangerous disease here, we review the scientific contributions and existing progress in developing sub unit vaccines, the role of molecular adjuvants; DNA vaccines, live delivery platform Attenuated vaccines developed to counteract virulent strains of *Yersinia-pestis*.

Keywords: *Yersinia pestis*, plague vaccine, Biowarfare agent, pneumonic plague, hematemesis

1. Introduction

Plague is caused by the facultative, intracellular gram negative bacterial pathogen, *Yersinia pestis* as one of the oldest and most notorious infectious disease plague's Notorienty came from the estimated 200 million deaths that were claimed throughout recorded human history and the extensive devastation that was imparted on societies which subsequently shaped the progress of human civilization. As a counter measure against the above scenarios it is imperative to develop a safe and efficacious vaccine against plague. In 2015, 15 human's cases of plague were reported in the US resulting in 4 deaths and in late 2017, the island of Madagascar had experienced a large outbreak of plague, where a total of 2348 confirmed probable and suspected cases of plague (70% are pneumonic form) occurred, including 202 deaths inciting regional panic. In recent year Modern molecular biological techniques have been applied to *Y-pestis* to construct strains with specific defined mutations designed to construct strains with specific defined mutations designed to create safe, immunogenic vaccines with potential for use in humans and as bait vaccines to reduce the load of *Y-pestis* in the environment, the plague is an infectious bacterial disease having a high fatality rate without treatment, referring to specific clinical symptoms of pulmonary plague the disease became known as the black death in the following years the role of rats and fleas and their detailed role in the transmission of plague has been discovered and experimentally verified.

Plague definition:

Plague is an infectious disease caused by the bacterium *Yersinia pestis*, symptoms include fever, weakness and headache. Usually this begins one to seven days after exposure these plague is spread by flea bites or handling an infected animal.

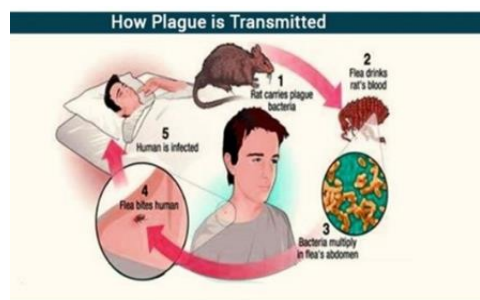


Fig. 1. How plague is transmitted

Types of plague: there are three basic forms of plague

1. Bubonic plague
2. Septicemic plague
3. Pneumonic plague

A. Bubonic plague

It is also called as black death a rare but serious bacterial infection that's transmitted by fleas. the bubonic plague is caused by the bacteria *Yersinia pestis*, it can spread through contact with infected fleas.



Oriental rat flea (*Xenopsylla cheopis*)

Fig. 2. Infected fleas

B. Extremely rare:

Fewer than 5 thousand cases per year

1. Treatable by a medical professional
2. Spread by animals or insects

3. Requires a medical diagnosis
4. Lab tests or imaging always required
5. Critical: needs emergency care.

Symptoms:

1. Swollen lymph nodes
2. Chicken eggs
3. Armpit, muscle ache
4. Fever, chills
5. Headache, fatigue

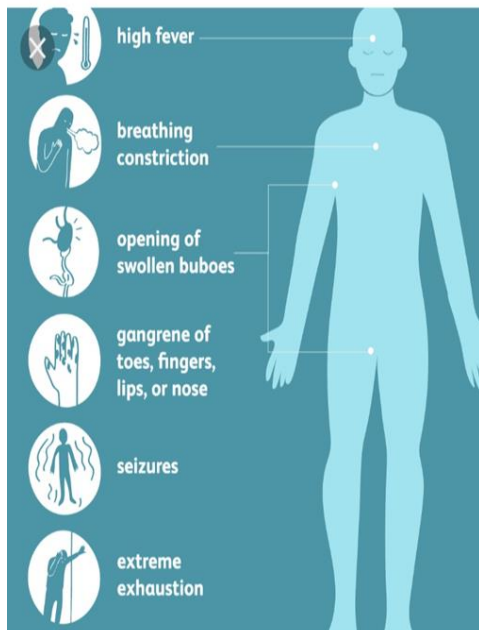


Fig. 3. Symptoms of bubonic plague



Treatment:

Bubonic plague requires urgent hospital treatment with antibiotics such as the amino glycosides, streptomycin and gentamicin, tetracycline (especially doxycycline)

Frequency: 650 cases reported a year

Diagnostic method: finding the bacteria in the blood, sputum or lymph nodes

2. Mechanism of Action

Bubonic plague is mainly spread by infected fleas from small animals. It may also result from exposure to the body

fluids from a dead plague- infected animal. In the bubonic form of plague the bacteria enter through the skin through a flea bite and travel via the lymphatic vessels to lymph nodes, causing it to swell

Prevention:

- Prevention is through public health measures such as not handling dead animals in area
- Vaccines have not been found to be very useful for plague prevention
- Without treatment, plague results in the death of 30% to 90% of those infected death, if it occurs is topically within 10 days.

A. Septicemic plague:

Septicemic plague is one of the three main forms of plague it is caused by *Yersinia pestis* a gram negative species of bacteria, septicemic plague is a life threatening infection of blood most commonly spread by bites from infected fleas like some other forms of gram negative species, septicemic plague can cause disseminated intravascular coagulation, and is almost always fatal when untreated. However, it only occurs in a minority of cases of *Yersinia* infection, so that fewer than 5000 people a year acquire the disease. It is the rarest of the plague

Sign and symptoms:

- The usual symptoms are,
- Abdominal pain
- Bleeding under skin due to blood clotting problems
- Bleeding from mouth, nose or rectum
- Diarrhea, fever
- Chills, low blood pressure
- Nausea, vomiting possibly blood
- Shock, organ failure
- Death of tissue (gangrene) causing blackening in extremities, mostly fingers toes and nose.

Causes, Transmission:

Human *Yersinia* infections most commonly result from the bite of an infected flea or occasionally on infected Mammal, but like most bacterial systemic diseases, this disease may be transmitted through an opening in the skin. However, the bacteria happen to enter the blood stream rather than the lymph or lungs, they multiply in the blood causing the bacteremia and severe sepsis.

In septicemic plague, bacterial endotoxins cause disseminated intravascular coagulation (DIC) Where tiny blood clots form throughout the body, commonly resulting in localized ischemic necrosis, tissue death from lack of circulation and perfusion

DIC results of the body's coping resources, so that it can no longer control bleeding consequently the un clotted blood bleeds into the skin and other organs leading to black or red patchy rash and to hematemesis or hemoptysis. The rash may cause bumps on the skin that look like insect bites, usually red, sometimes white in the center.

B. Other causes of septicemic plague

Septicemic plague is caused by horizontal and direct transmission. Horizontal transmission is the transmitting of a disease from one individual to another regardless of blood relation. Direct transmission occurs close physical contact with individuals through common air usage and direct bite from a flea or an infected rodents most common rodents may carry the bacteria and so may Leporidae such as rabbit

Significant carriers of the bacteria in the United states include:

- a) Rats
- b) Prairie dogs
- c) Squirrels
- d) Chipmunks
- e) Rabbits

The bacteria are cosmopolitan, mainly in rodents in all continents except Australia and Antarctica

The greatest frequency of human plague infections occurs in Africa mostly commonly seen in rural areas.

Diagnosis:

The following possible test could include

- i. Blood samples (detecting antibodies)
- ii. Culture samples of body fluids (check for the bacteria Yersinia Pestis)
- iii. Kidney and liver testing
- iv. Checking lymphatic system for sign of infection
- v. Checking for swelling
- vi. Checking for signs of dehydration
- vii. Checking for fever



Fig. 5. Septicemic plague diagnosis

Treatment:

Starting antibiotics early is a first step in treating septicemic plague in humans. One of the following antibiotics may be used

- Streptomycin
- Gentamicin
- Tetracycline or doxycycline
- Chloramphenicol

In animal's antibiotics such as Tetracycline or doxycycline can be used. Intravenous drip may be used to assist in dehydration

scenarios

Flea treatment can also be used

In some cases, euthanasia may be the best option for treatment and to prevent further spreading.

Pneumonic plague:

Pneumonic plague is severe lung infection caused by the bacterium Yersinia Pestis they typically start about 3 to 7 days after exposure. It is one of three forms of plague the other two being septicemic plague and bubonic plague.

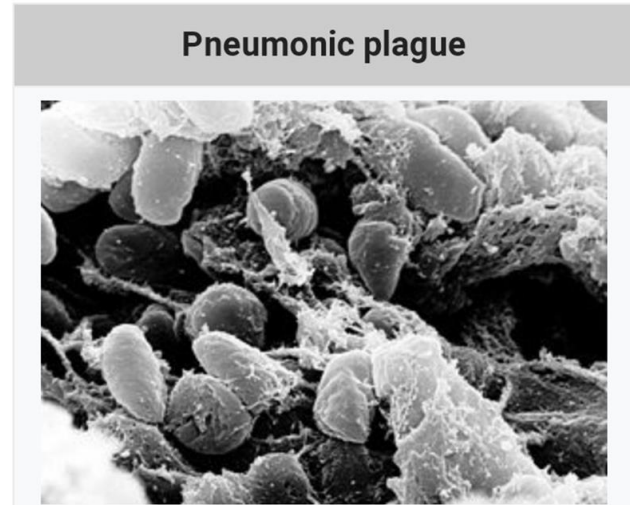


Fig. 6. Pneumonic plague

Symptoms:

- Fever
- Headache
- Shortness of breath
- Cough

Usual onset: 3 to 7 days

Causes: Yersinia pestis

Risk factor: Rodents

Diagnostic method:

Sputum testing

Treatment: Antibiotics

Frequency: Rare

The pneumonic form may occur following an initial bubonic or septicemic plague infection it may also result from breathing in air borne droplets from another person or cat infected with pneumonic plague. The difference between the forms of plague is the location of infection is in the lungs, in bubonic plague the lymph nodes

In septicemic plague with in the blood.

Diagnosis: Diagnosis is by testing the blood, sputum or fluid from a lymph node, while vaccines are being worked on, in most countries they are not yet commercially available.

Prevention:

Avoiding contact with infected rodents, people or cats. It is recommended that those infected be isolated from others.

Causes: Pneumonic plague can be caused in two ways

1. Primary

2. Secondary

Primary: Pneumonic plague can be caused in two ways primary

Which results from the inhalation of aerosolized plague bacteria

Secondary: When septicemic plague spreads into lung tissue from the blood stream, pneumonic plague is not exclusively vector borne like bubonic plague instead it can be spread from person to person it is also known as black death.

Treatment:

- a) Pneumonic plague is very aggressive infection requiring early treatment
- b) Antibiotics must be given within 24 hours of first symptoms to reduce the risk of death
- c) Streptomycin
- d) Gentamicin
- e) Tetracycline
- f) Chloramphenicol are all able to kill the causative bacterium
- g) Antibiotics treatment for 7 days will protect people who have had direct, close contact with infected patients wearing a close fitting surgical mask also protect against infection.

Mostly used common drug (doxycycline) for all types of plague.

C. Mechanism of Action

Doxycycline inhibits bacterial protein synthesis by binding to the 30s ribosomal subunit doxycycline has bacteriostatic activity against the broad range of gram positive and gram negative bacteria.

- i. Doxycycline side effects:
- ii. Loss of appetite
- iii. Nausea and vomiting
- iv. Diarrhea
- v. Rash
- vi. Sensitivity to the sun
- vii. Temporary discoloring of adult teeth
- viii. Weight loss

Doxycycline uses:

It is used for the antibiotic for the treatment of plague disease The newly invented plague vaccine used to treat the plague disease. Plague vaccine is a vaccine used against *Yersinia pestis* killed bacteria have been used since 1890 but are less effective against the pneumonic plague so that recently live vaccines of an Attenuated type and recombination protein vaccines have been developed to prevent this disease.

Modern vaccines for plague disease:

Attenuated Yersinia vaccine:

Lipoprotein NIPD of *Y-pestis* is an essential virulence factor for the development of bubonic and pneumonic plague.

Subcutaneous administration of the NIPD *Y-pestis* kimberlay 53 mutant conferred protection to mice against bubonic and pneumonic plague better than the EV 76 vaccine strain in comparison to the reference vaccine strain EVN11EG, immunization with the NIPD mutant strains provided potent

protective immunity against plague in BALB/C mice challenged with 200 LD of virulent *Y pestis* 231 strains NIPD *pestis* mutant as one of the live vaccine chopr's group characterized effects of the conserved quorum- sensing system on pulmonary *Y-pestis* infection in mice

Zauberman at all assessed whether immunization with the EV76 live vaccine can stimulate rapid and effective protective immunity against immediate challenge of virulent *Y-pestis* KIM53 strain.

Pseudo tuberculosis induced potent antibody and cell mediated response and significant TH17 response in mice, and more over provided significant protection against pulmonary challenge with high dose virulent *Y pestis* strains

High attenuation of *Y-pestis* 1pp MSBB plamutant in mice and rats, the strain was recently excluded from the centers for disease control and prevention select agent list

EV76 administration might promote rapid protection against pneumonic plague based on current studies vaccination with EV76 strain elicits a rapid and potent innate immune memory that could potentially provide considerable and immediate protection against bubonic and pneumonic plague, prior to mounting an adaptive immune response, which supports a novel therapeutic strategy for post outbreak emergency respoemerg Demeure's group and our group developed different Attenuated *Y-pseudo* tuberculosis either heterologous synthesizing capsule antigen F1 or delivering LCRV by type three secretion system

Protective efficacy and safety of these live Attenuated *Y-pseudo* tuberculosis strain should be evaluated further in other animal models al together those recent studies contribute to the growing evidences supporting development of live *Yersinia* vaccines as counter measures for preventing plague.

D. Subunit plague

Mainly studies have established that the low calcium response protein v (LCRV), a multi-functional virulence protein, is an indispensable protective antigen against *Y- pestis* infection RYP VaxTm manufactured by pharm athene Inc. was a recombinant plague vaccine comprising separate FI (RFI) and v (RV) antigens produced in *Escherichia coli* the rf1- v fusion vaccine was developed by the United states army medical research institute for in fection currently being further developed by Dynport vaccine company, LLC RF1 -v and RV10 vaccine were unable to protect African green monkeys against pneumonic plague uniformly as cynomolgus macaques, despite eliciting robust antibody response. The in consistent efficacy of these subunit vaccine in African green monkeys and cynomolgus macaques was speculated to be due to a deficiency in innate or cellular immunity resulting in a lack of effective synergistic action between humoral and cell mediated immune response to defined against pneumonic plague.

Intramuscular injection of flagellin (F1) v in a dose escalation manner was conducted in healthy individuals from aged through 45 years in a phase 1 trail. 60 healthy subjects were enrolled 52% males, 100% non-Hispanic, 91.7 % white and

mean age 30.8 years' positive antibody responses were observed to F1, V1 and flaelin with no severe Reactogenicity.

Rao's group has developed a RF1 mutv-PA recombinant subunit vaccine consisting of Y-pestis F1 and LCRV dual antigens, and bacillus anthracis protective antigen (PA) adjuvants with al hydrogel the trivalent vaccine elicited robust and conferred complete protection in mice, rats and rabbits against simultaneously intra nasal (I N) challenge with Y-pestis co92 and lethal intra venous (I.V) injection of B. anthracis toxin

Vyp wax duo is a novel vaccine developed by moore at al approached their vaccine design with the goal of creating practical solution for low and middle income countries endemic to plague vypvax duo is a strong potential vaccine as the primary vaccine formulation under thermo stressed conditions, circumventing the need for a cold chain for distribution and storage.

Novel subunit plague vaccine developed by liv et al is composed of a native F1 and recombinant v (F1+RV) antigens absorbed to aluminum hydroxide adjuvant the F1+Rv vaccine induced a very strong humoral immune response and a low level of cell mediated immune response in cynomolgus macaques, subsequently

The national institutes for food and drug control (NIOFDC) and the Jiangsu provincial centers for disease control and prevention (CDC) conducted a one year immunogenicity and vaccine safety study where 240 healthy adults aged 18-55 years were F1+Rv immunized with 15mg at day or 20mg at day 28 results showed that anti-F1 titers Sero conversion rates were maintained at high levels up to 12 months while anti-v titers and sero conversion rates decreased sharply at 6 months and continued, decrease at 12 months no vaccine related serious adverse events were observed during immunization.

Overall human clinical trials show the F1+Rv subunit vaccine induced a robust humoral immune response up to 12 months and has good safety profile in humans.

Monoclonal antibodies as therapeutic vaccines:

Previous studies showed that anti- LCRV or F1 monoclonal antibodies (MABS) can passively protect mice against plague challenge Intercheal delivery of aerosolized LCRV specific and F1-specific monoclonal antibodies (MABS 7 3 and F1-04-A-G) protect mice in a model of pneumonic plague three of the MABS (F5 C10, F6 E5 and F2 H5) provided different levels of protection in mice subconsciously challenged with 600 CFU of Y-pestis 14 among then, F2 H5 provided complete protection in balb/c mice. Subcutaneously challenged with Y-pestis 141 strain collectively, it would be possible that MABS specific to F1 or LCRV can be utilized as a fast acting post exposure treatment for humans against Y-pestis infection.

Live vectored plague vaccines: An improved recombinant Attenuated salmonella typhimurium vaccine strain expressing multiple plasmid encoded Y-pestis antigens, including LCRV 196 (aa residues 131-326) psn (pestisin receptor) and F1 has been studied by our group high antibody titers specific for RLCVP, PSN, and F1 were developed oral immunization with

x12094 (pyA5383) did not caused any death or disease symptoms in SCID mice over a 60- days period. horwitz's group investigated an F. tularensis LVS cap B mutant strain and an Attenuated listeria monocytogenes strains as vectors to deliver multiple protective antigens from B. anthracis and Yersinia pestis as a novel vaccine plat form this study provided a proof concept for an all in one vaccine providing protection against several tier 1 pathogens simultaneously only the TMV – conjugated LCRV or F1 now protected against subsequent lethal challenge with Yersinia pestis these results suggests that mucosal delivery of TMV synthesizing F1 – LCRV might induce complete protection against a lethal pneumonic infection of Yersinia pestis in mice, researchers at the United states geological survey national wildlife health center have developed a sylvatic plague vaccine (SPV) comprised of raccoon pox virus expressing both F1 and + runcated protein antigens, designed as a bait vaccine to protect prairie dogs, prairie dogs are highly susceptible to Yersinia pestis and as such are potential sources of plague transmission to humans.

Whole cell based vaccines against plague:

The idea to develop vaccine against plague started by Alexander Yersin in 1895 against Yersinia pestis in small animal models in laboratory. He evaluated heat- killed whole cell vaccine this finding encouraged researchers to develop two types of vaccines.

- Killed whole cell (K. W .C)
- Live whole cell (L. W. C)

These vaccines were found safe and evoked immunity against bubonic plague but found inefficient against pneumonic plague, these types of vaccines were able to induce strong immune response against both bubonic and pneumonic plague.

E. Future perspectives:

The F1/LCRV based subunit vaccine mainly induces humoral immune response while this vaccine has shown promising results in animal models, it's protective potential in humans is yet to be assessed in the near future the F1/LCRV base vaccine may be accessible to population residing in plague endemic areas, Next generation plague vaccine should be designed to stimulate strong cell mediated immunity as well both the responses humoral and cellular effectively contribute to vaccine efficiency.

3. Conclusion

The conclusion is that the article was conducted to discover the new type of vaccines in world to reduce the plague diseases by the Yersinia pestis vaccine F1/LCRV vaccine. Provides strong protective immunity in mice, rats and rabbits against subcutaneous and pneumonic plague.

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