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MORBIDITY AND MORTALITY WEEKLY REPORT

Prevention of Plague

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Centers for Disease Control
and Prevention (CDC)
Atlanta, Georgia 30333



The *MMWR* series of publications is published by the Epidemiology Program Office, Centers for Disease Control and Prevention (CDC), Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA 30333.

SUGGESTED CITATION

Centers for Disease Control and Prevention. Prevention of plague: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1996;45(No. RR-14):[inclusive page numbers].

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Copies can be purchased from Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325. Telephone: (202) 512-1800.

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Prevention of Plague: Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Summary

These revised recommendations by the Advisory Committee on Immunization Practices concerning prevention of plague update previous recommendations (MMWR 1982;31:301–4). This report includes information and recommendations on vaccination, public health practices, and medical treatment to prevent plague among humans.

INTRODUCTION

Plague is an acute, often fatal, and potentially epidemic disease caused by infection with *Yersinia pestis*. Plague exists in natural enzootic cycles involving wild rodents and their fleas in certain regions of Asia, Africa, the Americas, and extreme southeastern Europe near the Caspian Sea (Figure 1). These natural cycles may be inapparent, with no transmission to humans, or associated with sporadic transmission to humans. Epidemics of plague occasionally occur when the disease spreads from wild rodents into populations of rats (genus *Rattus*) that live near human habitation. Because of the high case-fatality rate and the epidemic potential of this disease, plague is designated a Class I notifiable disease and thus is subject to International Health Regulations. These regulations require that all suspected cases be reported to and investigated by public health authorities and that confirmed cases be reported to the World Health Organization (WHO) in Geneva, Switzerland. In the United States, suspected cases of plague should be reported to state health departments, which in turn notify CDC. All cases subsequently confirmed by laboratory analysis are reported by CDC to WHO.

CHARACTERISTICS OF PLAGUE

Etiologic Agent

Y. pestis is a gram-negative coccobacillus belonging to the *Enterobacteriaceae*. This bacterium has several chromosomal and plasmid-associated factors that are essential to its virulence and survival in mammalian hosts and flea vectors (1,2).

Modes of Transmission and Description of Disease

The most common mode of transmission of *Y. pestis* to humans is by the bite of infectious fleas. Less frequently, infection is caused by a) direct contact with infectious body fluids or tissues while handling an infected animal or b) inhaling infectious respiratory droplets or other infectious materials (e.g., laboratory-generated aerosols containing *Y. pestis*). Infection causes a severe febrile illness characterized by headache, myalgia, malaise, shaking chills, prostration, and gastrointestinal symptoms.

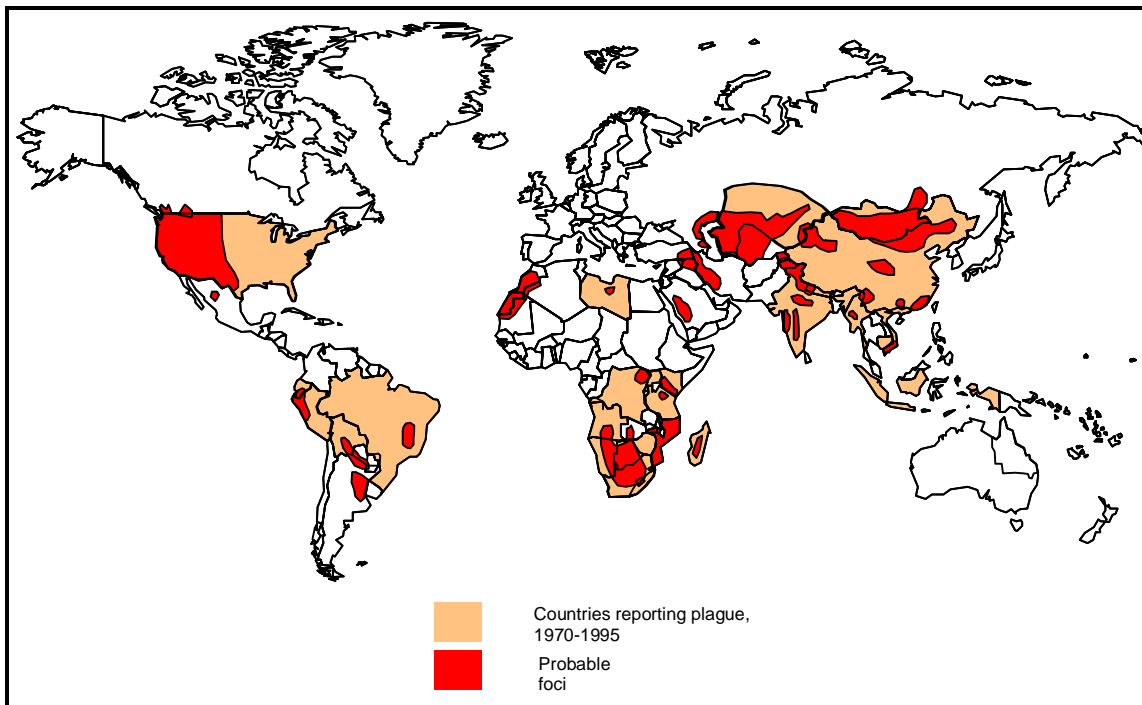
The three principal clinical presentations of plague are bubonic, septicemic, and pneumonic.

Bubonic plague, characterized by development of an acute regional lymphadenopathy, or bubo, is the most common clinical form of disease, accounting for 80%–90% of cases in the United States. Buboes typically involve lymph nodes that drain the site of initial infection and are most often located in the inguinal, axillary, or cervical regions (3,4). The incubation period for bubonic plague usually ranges from and rarely exceeds 2 to 6 days. The case-fatality rate for infected persons who are not treated is 50%–60% (3).

Septicemic plague, which occurs when *Y. pestis* invades and continues to multiply in the bloodstream, can occur secondarily to bubonic plague or can develop without detectable lymphadenopathy (i.e., primary septicemic plague) (3–5). In the United States during 1947–1977, approximately 10% of plague patients presented with septicemic plague; approximately 50% of these persons died as a result of disease (3). Complications of this form of plague include septic shock, consumptive coagulopathy, meningitis, and coma (3).

Pneumonic plague is the least common but most dangerous and fatal form of the disease. It can develop as a secondary complication of septicemic plague or result from inhalation of infectious respiratory droplets expelled from a human or animal that has plague pneumonia. Signs of pneumonic plague include severe pneumonia accompanied by high fever, dyspnea, and often hemoptysis. The incubation period for primary pneumonic plague is 1–3 days. Patients who do not receive adequate treatment within 18 hours after onset of respiratory symptoms are unlikely to survive (3).

FIGURE 1. Distribution of natural foci of plague*



*Compiled from the World Health Organization, CDC, and other sources.

Ecology

Y. pestis is maintained in complex enzootic and epizootic transmission cycles involving susceptible wild rodents and their fleas (3,6). Risk for plague in humans is greatest when epizootics cause high mortality in commensal rat populations, thereby forcing infected rat fleas (*Xenopsylla cheopis*) to seek alternative hosts, including humans. These episodes of high mortality among rats do not contribute to maintenance of *Y. pestis* in nature (3). Other animals, including carnivores and rabbits, occasionally become infected with *Y. pestis* but are only incidental hosts. However, carnivores may contribute to the transfer of infected fleas from one geographic area to another (7).

Epidemiology

During 1980–1994, a total of 18,739 cases of plague in humans were reported to WHO from 20 countries (average: 1,087 cases per year) (Table 1) (8). Plague is underreported in many countries, particularly those in which surveillance and laboratory capabilities are inadequate. Epidemics are most likely to occur in areas that have poor sanitary conditions and large populations of rats. Isolated cases in humans also can

TABLE 1. Reported cases of plague in humans, by country—1980–1994*

Continent	Country	No. of cases	No. of deaths
Africa	Angola	27	4
	Botswana	173	12
	Kenya	49	10
	Libya	8	0
	Madagascar	1,390	302
	Malawi	9	0
	Mozambique	216	3
	South Africa	19	1
	Tanzania	4,964	419
	Uganda	660	48
	Zaire	2,242	513
	Zambia	1	1
	Zimbabwe	397	1
	Total	10,155	1,344
America	Bolivia	189	27
	Brazil	700	9
	Ecuador	83	3
	Peru	1,722	112
	United States	229	33
		Total	2,923
Asia	China	252	76
	India	876	54
	Kazakhstan	10	4
	Mongolia	59	19
	Myanmar	1,160	14
	Vietnam	3,304	158
		Total	5,661
World Total		18,739	1,853

*World Health Organization. Human plague in 1994. Wkly Epidemiol Rec 1996;22:165–72.

result from exposure to infected wild or domestic animals or their fleas. Outbreaks of plague have been reported recently from Africa, Asia, and South America (8).

In the United States, 341 cases of plague in humans were reported to CDC during 1970–1995 (average: 13 cases per year) (Figure 2). Of these cases, 80% occurred in the southwestern states of New Mexico, Arizona, and Colorado (9,10; CDC, unpublished data). Another 9% of cases were reported from California. Nine other western states reported limited numbers of cases. Modes of transmission were determined for 284 of these case-patients and included flea bite* (n=222; 78%); direct contact with infected animals (n=56; 20%); and inhalation of infectious respiratory droplets or other airborne materials from infected animals (n=7; 2%). Five of the seven persons who were infected by inhalation were exposed to infected domestic cats, and a sixth person (a veterinarian) also may have had such an exposure.

In the United States, most cases of plague in humans occur in the summer months, when risk for exposure to infected fleas is greatest. The majority of these cases, especially those in the Southwest, are acquired in or near the patient's residence (9,10). Risks for acquiring the disease are associated with conditions that provide food and shelter for plague-susceptible rodents near human dwellings (6,9–12). Less often, plague is acquired while working or while participating in recreational activities, the latter having occurred most often among patients from California (13).

PLAGUE VACCINE

History of Plague Vaccines

Killed bacteria have been used in plague vaccines since 1896. However, only one vaccine—a formalin-inactivated preparation—is currently licensed for use in the United States. This vaccine (plague vaccine, USP) was manufactured by Cutter Biologicals (a division of Miles Laboratories, Inc.) but is now available only from Greer Laboratories, Inc. The killed or inactivated plague vaccine is prepared from *Y. pestis* organisms grown in artificial media and then inactivated in formaldehyde. The inactivated bacteria are suspended in a 0.9% sodium chloride solution at a concentration of 1.8 to 2.2 x 10⁹ bacteria per mL of vaccine. The vaccine also contains trace amounts of media components (e.g., beef-heart infusion, soytone [or phytone], casamino acids, sodium sulfite [Na₂SO₃], L-cysteine hydrochloride, and yeast extract) and 0.5% phenol as a preservative.

Live *Y. pestis* vaccines composed of presumably avirulent strains also have been developed (14). However, none of these vaccines is commercially available, and their safety and efficacy have not been adequately tested.

Immunogenicity and Efficacy

The efficacy of the inactivated plague vaccine in humans has not been measured in controlled studies. Completion of such studies in the United States is unlikely because of the low incidence of plague in this country. A retrospective study of U.S. military personnel who served in Vietnam provides some indirect evidence for the efficacy of the inactivated vaccine (manufactured by Cutter Laboratories) in preventing

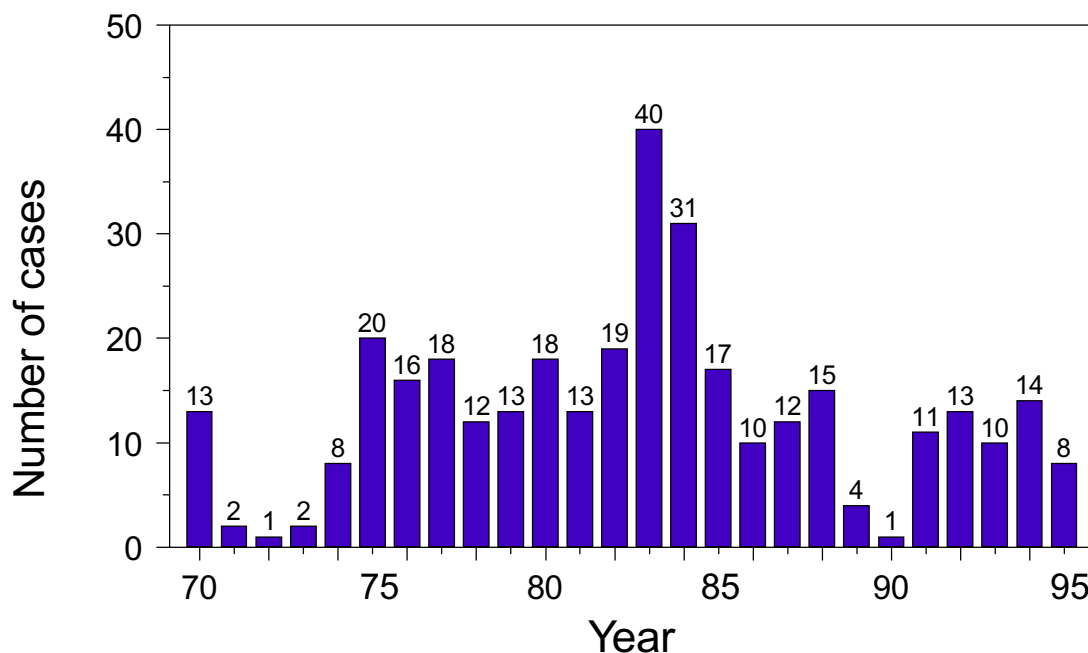
*Persons who develop inguinal buboes or recall being bitten by fleas are considered to have been infected via flea bite.

flea-borne plague (15). During 1961–1971, only eight cases of plague were diagnosed among U.S. personnel in Vietnam who had received plague vaccine (i.e., one case per 10^6 person-years of exposure). U.S. military personnel in Vietnam were considered to be at risk for exposure to *Y. pestis*-infected fleas because a) many military personnel developed murine typhus, which is a rickettsial disease transmitted by the same rat flea (*X. cheopis*) that is the primary vector of plague in Vietnam; b) thousands of cases of plague occurred among Vietnamese civilians during 1961–1971 (333 cases per 10^6 person-years of exposure [16]); c) plague was commonly identified in rodent populations on or near U.S. military installations; and d) fourfold rises in antibody titer to *Y. pestis* were identified in four murine typhus patients who previously had had low passive-hemagglutination (PHA) titers as a result of vaccination and in another three persons who had had no detectable levels of antibody in acute-phase serum samples. Such evidence suggests exposure to both *Rickettsia typhi* (formerly *Rickettsia mooseri*) and *Y. pestis*.

Researchers have not determined whether vaccination protects against infectious droplets or aerosols generated in laboratories or against exposure to infectious respiratory droplets from patients who have pneumonic plague. At least two persons vaccinated with a previous formulation of the inactivated vaccine contracted pneumonic plague following exposure to *Y. pestis* (17,18). Whether these cases developed after the patients inhaled infectious droplets or as complications of septicemic plague was not reported. Persons potentially exposed to patients who have pneumonic plague or to *Y. pestis* aerosols in the laboratory should be administered a 7-day course of antimicrobial therapy, regardless of vaccination history. Antimicrobials recommended for prophylaxis include tetracycline, doxycycline, or trimethoprim-sulfamethoxazole (19).

Laboratory studies involving animals suggest that induction of antibodies to the fraction 1 capsular antigen (F1) of *Y. pestis* following vaccination is a strong indicator

FIGURE 2. Reported cases of human plague, United States—1970–1995



of protection (18,20–25). Data from one study indicated that 90% of rats that had anti-F1 titers ≥ 128 by PHA survived injection with 1×10^3 to 5×10^5 virulent *Y. pestis*, compared with 46% of rats with titers of 32–64 and 6% of rats with titers of ≤ 16 (24). Data from other studies reveal that 11 of 14 Hanuman langurs and six of seven African green vervets that had anti-F1 titers ≥ 128 survived similar challenges (18,24,26,27). Mice vaccinated with F1 antigen expressed by a recombinant *Escherichia coli* clone containing the F1 gene of *Y. pestis* also were protected against challenge by virulent *Y. pestis* (28). Although data from previous studies have correlated the induction of adequate anti-F1 antibody titers with protection against plague, recent data indicate that immune responses to other *Y. pestis* antigens (e.g., V antigen) also might provide protection in laboratory animals (29). The extent to which plague vaccine induces such immune responses, however, has not been adequately determined.

Studies of passively immunized animals also suggest that an anti-F1 titer ≥ 128 is protective (18). For these indirect potency tests, sera (0.5 mL) from immunized mice, guinea pigs, monkeys, or humans are injected into 10 test mice. The object of this indirect mouse potency test is to determine whether anti-F1 antibodies present in the sera of the immunized animals protects the recipient mice from a subcutaneous challenge with virulent *Y. pestis* (20,30,31). Results are expressed as a mouse protection index (MPI), which is calculated by dividing the percentage of mortality among the 10 test mice by the average day of death (20,30). The lower the index, the greater the level of protection; MPIs ≤ 10 are considered protective (18).

Data concerning protective antibodies in humans are limited. Data from one study indicated that 15 of 23 persons vaccinated with two doses of inactivated plague vaccine (manufactured by Cutter Biologicals) developed antibodies that were protective for mice (i.e., MPI ≤ 10) (18). A second study examined serum antibody levels among 29 persons who were administered three injections of the same vaccine (1.0 mL for the initial vaccination and 0.2 mL for vaccination 90 and 270 days later); 90% of vaccinees had detectable PHA titers within 15 days after the second injection, and 93% had such titers within 4 days after the third injection (20). The titers for each of the 29 vaccinees were not reported, but serum samples from five vaccine recipients who had titers ≥ 128 yielded MPI values ≤ 10 . Serum samples from five subjects who had PHA titers < 128 did not protect mice in potency tests (20).

Data from another study of 117 military personnel who received multiple doses of the inactivated plague vaccine (manufactured by Cutter Biologicals) indicated that 84 (72%) developed PHA titers ranging from 1,024 to 16,382, a total of 23 (20%) had titers from 64 to 512, and nine (8%) did not develop a titer in response to vaccine (32). Each of these 117 persons had received an initial series of three injections, followed by repeated booster injections at about 6-month intervals (average: five booster doses per person). Serum samples from 16 of these persons were tested in indirect mouse potency tests. All six vaccinees with PHA titers < 128 had MPI values > 10 , and four of the 10 subjects with titers ≥ 128 had MPIs ≤ 10 .

A recent study conducted among U.S. military personnel compared MPI values in serum samples from four groups: persons vaccinated with one of three different lots of the inactivated vaccine manufactured by Greer Laboratories and a fourth group of persons administered the vaccine formerly marketed by Cutter Biologicals (Table 2) (Greer Laboratories, Inc., unpublished data). Subjects were vaccinated with two doses approximately 30 days apart. Humoral immune responses were measured in serum

samples obtained 4 weeks after the second dose. Indirect potency tests demonstrated protective levels of antibody (MPI values ≤ 10) in sera of only 55%–58% of vaccinees. MPI values did not differ significantly by vaccine lot or manufacturer.

Vaccine Administration

Indications

Persons should be vaccinated only if they are at high risk for exposure. Thus, vaccine is recommended for persons in the following high-risk groups:

- laboratory personnel who routinely perform procedures that involve viable *Y. pestis*; and
- persons (e.g., mammalogists, ecologists, and other field workers) who have regular contact with wild rodents or their fleas in areas in which plague is enzootic or epizootic.

All vaccinated persons should follow the preventive measures discussed in this report because of uncertainties about the efficacy of the vaccine (see Alternatives to Vaccination and Supplemental Protection). If vaccinees are believed to have been exposed to plague or if their risk for exposure is exceptionally high, prophylactic antibiotic use should be considered as a supplement to vaccination. Vaccination is not intended as a method of controlling plague epidemics because several months are required to complete the primary vaccination series and to develop adequate levels of protective antibodies.

Routine vaccination is not necessary for persons living in areas in which plague is enzootic (e.g., the western United States). Vaccination is not indicated for hospital staff or other medical personnel in such areas, nor for most travelers to countries in which cases of plague have been reported,* particularly if their itineraries are limited to urban areas and modern hotel accommodations.

*For a current listing of countries, consult the most recent issue of WHO's *Weekly Epidemiological Record*. Current information also is available from the Division of Quarantine, National Center for Infectious Diseases (NCID) (telephone: [404] 639-8100) or from the Division of Vector-Borne Infectious Diseases, NCID (telephone: [970] 221-6400).

TABLE 2. Mouse protection index (MPI) values for serum samples collected from human vaccinees who were administered two doses of plague vaccine*†

Manufacturer	Lot no.	No. of subjects	Geometric mean MPI	MPI values	Percentage of protective MPIs [§]
Cutter	1	22	8.88	1.7–18.9	45
Greer	1	19	8.69	0.0–17.9	58
	2	20	9.84	0.0–20.8	55
	3	20	8.92	0.0–17.9	55

*Initial dose=1.0 mL; second dose=0.2 mL. The second dose was administered approximately 30 days after the first; sera were tested 57–58 days after the first injection.

†Greer laboratories, Inc., unpublished data.

§MPIs ≤ 10 are considered protective.

Supply and Storage

Plague vaccine is manufactured by Greer Laboratories, Inc., P.O. Box 800, Lenoir, N.C. 28645-0800. The vaccine is shipped refrigerated in 20-mL vials and should be stored at 35–46 F (2–8 C). The vaccine should not be frozen.

Primary Vaccination

All injections should be administered intramuscularly, preferably in a deltoid muscle. Primary vaccination consists of a series of three injections (Table 3). Recommended dosages are available only for persons 18–61 years of age; dosage recommendations for other age groups have not been formulated because data are insufficient. No published data are available concerning the interactions of plague vaccine with drugs or other biologics administered concurrently. The simultaneous administration of plague vaccine with other vaccines that are likely to be reactogenic should be avoided.

Booster Doses and Monitoring Antibody Levels

The proportion of vaccinees whose serum produces an MPI ≤ 10 in the indirect mouse potency test after three doses of vaccine is unknown. PHA antibody titers decrease soon after vaccination and could drop below the presumably protective level of 128 within a few months (20). Booster doses of 0.2 mL each can be administered three times at approximately 6-month intervals when vaccinees have continuing high risk for exposure, especially for those persons who have PHA titers of <128 . Additional booster doses can be administered at 1- to 2-year intervals to persons who remain at risk for infection. Persons considering being vaccinated should be advised that they may have difficulty having their PHA titers evaluated because only a few public health and research laboratories routinely perform this test.

Adverse Reactions

Adverse reactions following injection of the first dose of plague vaccine generally are mild, but the frequency and severity of such events can increase with repeated doses (33). Common adverse reactions include local erythema and induration at the site of injection, malaise, headache, fever, and lymphadenopathy (14). These reactions usually do not persist for >48 hours.

Severe reactions to plague vaccine occur in a limited number of recipients, most often in persons who receive repeated doses (33). Data regarding adverse reactions have been obtained largely from a study conducted during 1950–1971 that examined 1,219 persons who received a total of 18,751 injections (including primary-series and booster doses) of one or more of three different formalin-inactivated vaccine

TABLE 3. Recommended dosages of plague vaccine for primary vaccination of persons 18–61* years of age

Dose number	Amount (mL)	Recommended time of injection
1	1.0	NA [†]
2	0.2	1–3 months after first injection
3	0.2	5–6 months after second injection

* Recommendations are not given for other age groups because data are insufficient.

[†]Not applicable.

preparations (manufactured by Cutter Biologicals) (33). These preparations differed primarily in the growth media, strains of *Y. pestis*, and methods of standardization used in their preparation. The most recent of these three vaccine preparations, used during 1967–1971, was produced using essentially the same methods as the current Greer Laboratories vaccine.

Although some local reactions (i.e., edema, induration at the site of injection, or both) were observed in 29% of the study population, moderately severe to severe local reactions were rare (occurring after 0.15% of injections). Severe local reactions included various combinations of a) >12-cm edema and/or induration; b) inflammatory involvement of elbow, forearm, and/or clavicular fossa; and c) inflammation causing >50% limitation of use of the arm. Seven (0.04%) additional injections resulted in immediate reactions characterized by transient swelling and redness radiating from the injection site. Six of these seven reactions occurred in the same person. Twenty percent of vaccine recipients had some systemic reactions (e.g., malaise, mild headache, generalized myalgia and arthralgia, fever, chills, and nausea). Of the 18,751 individual injections administered during the study, 68 resulted in severe systemic reactions (0.4% of total injections) that were characterized by one or more of the following manifestations: severe headache, generalized myalgia and arthralgia, malaise, nausea and vomiting, diarrhea, shaking chills, and oral temperatures ≥ 101 F (≥ 38 C). Fourteen instances of anaphylaxis (0.07% of total injections) also were reported and were characterized by urticaria, bronchospasm, and hypotension. Anaphylaxis occurred within 30 minutes of inoculation and was of short duration because patients received prompt medical treatment.

Fifty-three persons received only the more recently manufactured vaccine preparation, which is similar to the current Greer Laboratories vaccine. Local reactions occurred in 3% of persons who received this vaccine; 1% of persons had systemic reactions. Information regarding the severity of the local and systematic reactions occurring in this group was not reported. Although a few reports of sterile abscesses occurring following administration of plague vaccine were received by the former manufacturer (Cutter Biologicals), no such abscesses were identified in this study (Greer Laboratories, Inc., plague vaccine package insert).

Plague vaccine has not been reported to cause death; however, one person who had a history of idiopathic anaphylaxis died several hours after receiving a third dose of plague vaccine (34). This person also had received Japanese encephalitis vaccine 2 days before death. The cause of death was not identified at autopsy.

The frequency and severity of adverse reactions among military personnel 18–61 years of age who were administered the current Greer Laboratories vaccine are comparable to those previously reported for the Cutter Biologicals vaccine (Greer Laboratories, Inc., unpublished data). Persons who were administered vaccine manufactured by Greer Laboratories were initially injected with a 1.0-mL dose and then were administered a second, 0.2-mL dose 30 days later (Table 4). Adverse reactions generally were mild and transient and occurred less frequently after the second 0.2-mL injection than after the initial 1.0-mL dose (Table 4). No data concerning adverse events are available for the third primary dose or for booster injections of the Greer Laboratories vaccine.

Adverse reactions should be reported to the Vaccine Adverse Event Reporting System (VAERS). VAERS reporting forms and information can be obtained by calling (800) 822-7967.

Precautions and Contraindications

Precautions to prevent adverse reactions should include review of the vaccinee's history of hypersensitivity to plague vaccine and its components. Epinephrine should be available for immediate use in the event of anaphylaxis or other allergic reactions to the vaccine.

The safety and immunogenicity of the vaccine for persons <18 years of age have not been evaluated. The effects of plague vaccine on the developing fetus also are unknown. Pregnant women who cannot avoid high-risk situations should be advised of risk-reduction practices and should be vaccinated only if the potential benefits of vaccination outweigh potential risks to the fetus.

Persons who are immunocompromised or who are receiving immunosuppressive therapy may not develop protective levels of antibody following vaccination. Whenever possible, antibody levels determined by PHA should be obtained to determine whether additional doses beyond the primary series should be administered.

Plague vaccine should not be administered to persons who have a history of hypersensitivity to the vaccine or its components. Persons who have an acute febrile illness (e.g., influenza) should not be vaccinated until they have recovered fully.

TABLE 4. Percentage of vaccine recipients reporting local and systemic reactions occurring within 48 hours of vaccination with inactivated plague vaccine*†

Reaction	Percentage of recipients	
	Dose 1 [§] (N=67)	Dose 2 [¶] (N=59)
Local		
Tenderness	71.6	18.6
Decreased arm motion	11.9	1.7
Erythema	4.5	0.0
Warmth	3.0	1.7
Edema	1.5	0.0
Systemic		
Headache	19.4	6.8
Nausea	13.4	3.4
Malaise	10.4	5.1
Dizziness	6.0	0.0
Chills	4.5	3.4
Joint ache	4.5	0.0
Muscle ache	4.5	0.0
Anorexia	1.5	0.0
Diarrhea	1.5	0.0
Vomiting	1.5	0.0

* Greer Laboratories, Inc.

† Among adults 18-61 years of age.

§ Vaccinees received 1.0 mL of vaccine.

¶ Vaccinees received 0.2 mL of vaccine, which was administered 30 days after dose 1.

ALTERNATIVES TO VACCINATION AND SUPPLEMENTAL PROTECTION

Vaccination is usually unnecessary when appropriate preventive measures are taken. Vaccinated persons should follow the preventive measures discussed in the following sections because of uncertainties about the efficacy of plague vaccine.

Residents of Areas in Which Plague Is Endemic

In the western United States, most persons with plague become infected when rodent plague epizootics occur near their residences. Recommended means of reducing the risk for acquiring plague in and around homes include a) eliminating sources of food and shelter for rodents near homes, b) modifying homes to prevent rodent access, c) treating domestic dogs and cats weekly with appropriate insecticides, d) avoiding direct contact with sick or dead rodents, and e) handling severely ill cats with extreme caution (these animals should be examined by a veterinarian).

Persons Who Participate in Outdoor Activities

Hikers, campers, and other persons who participate in outdoor recreational activities in areas where plague is endemic should a) avoid handling sick or dead animals, b) avoid rodent nests and burrows, c) use insect repellents containing N, N-diethyl-m-toluamide (DEET) on skin and repellents or appropriate insecticidal sprays on clothing, and d) treat accompanying pets with appropriate insecticides. Hunters should always wear gloves when handling dead animals.

Medical Personnel and Persons Having Close Contact with Infected Persons

Persons suspected of having pneumonic plague should be maintained under respiratory droplet precautions for 48 hours after antibiotic treatment begins (35). Persons who have confirmed cases of pneumonic plague should be kept under droplet precautions until sputum cultures are negative (35,36). Patients in whom pneumonic plague has been excluded warrant standard precautions only (35). Prophylactic antibiotics should be administered to persons who have had close exposure (i.e., within 6.5 feet [2 meters]) to persons suspected of having pneumonic plague (Table 5) (19,36). Persons who have not had such exposure are unlikely to become infected but should be monitored closely.

Laboratory Workers

Routine bacteriologic work involving plague can be performed in biosafety level 2 laboratories. Standard precautions (e.g., the use of a biological safety cabinet to contain aerosols that are generated unintentionally) are sufficient to prevent clinical laboratory workers from being infected with *Y. pestis*. Few laboratory-associated cases have been reported; these cases have involved unusual exposures in clinical diagnostic laboratories or in laboratories that conduct research involving live *Y. pestis* (37).

Persons Who Work with Potentially Infected Animals

These workers should be informed on how to minimize their exposure to the tissues and fleas of potentially infective animals. Precautionary measures include a) avoiding areas where high mortality in commensal rat populations has been observed, b) wearing gloves when handling animals, c) applying insect repellents containing DEET to clothes and skin, and d) treating clothes with appropriate insecticides.

Persons Who Work in Veterinary Clinics

Persons working in veterinary practices in areas where plague is enzootic should be educated on the risks of handling cats infected with *Y. pestis*. Such persons should wear gloves and eye protection and take appropriate respiratory precautions when examining cats that have fever and obvious acute lymphadenopathy, oral lesions, or pneumonia (9).

Persons Living, Working, or Traveling in Other Countries

In most countries of Africa, Asia, and South America in which plague is enzootic, the risk for acquiring plague is greatest in semiarid grassland or mountainous areas. The likelihood of plague spreading from wild-rodent foci into village or urban centers is greatest when a) environmental conditions precipitate an increase in or movement

TABLE 5. Recommendations for prophylactic antimicrobial therapy for persons exposed to *Yersinia pestis*,* by agent and age

Antimicrobial agent	Age	Dosage
Tetracycline [†]	Adults [§]	2 g/day in two or four equal doses at 12- or 6-hour intervals for 7 days, by mouth
	Children [¶]	25–50 mg/kg/day in two or four equal doses at 12- or 6-hour intervals, respectively, for 7 days, by mouth
Doxycycline	Adults [§]	100–200 mg/day in two equal doses at 12-hour intervals for 7 days, by mouth
	Children [¶]	2–4 mg/kg/day in two equal doses at 12-hour intervals for 7 days, by mouth
Trimethoprim-sulfamethoxazole	Adults [§]	1.6–3.2 g/day sulfamethoxazole component in two equal doses at 12-hour intervals for 7 days, by mouth
	Children ^{**}	40 mg/kg/day sulfamethoxazole component in two equal doses at 12-hour intervals for 7 days, by mouth

*Information is for single exposures. Prolonged use of antimicrobial prophylaxis should be supervised by a physician in consultation with public health officials.

[†]Use of tetracycline during pregnancy should be avoided.

[§]Persons ≥18 years of age.

[¶]Persons 9–17 years of age.

**Persons ≥2 months to 18 years of age.

of rodent populations, thus leading to increased population densities of plague-susceptible rodents and their fleas or b) natural disasters or other events interrupt routine sanitary practices. Whenever possible, persons living in regions where plague is enzootic should avoid rodent-infested locations, especially if unusually high numbers of dead rodents have been reported. Persons who must work in such areas should avoid handling sick and dead rodents and use repellents and appropriate insecticides to reduce their risk for being bitten by fleas. Travelers to plague-endemic areas generally are at low risk for infection with *Y. pestis*. Persons who travel to these areas should avoid rat-infested sites with recently reported cases of plague among humans, especially those sites at which dead rats have been observed. To reduce the likelihood of being bitten by fleas, travelers can apply insect repellents to skin and repellents and insecticides to clothing and outer bedding. Short-term prophylactic use of antibiotics should be considered only for circumstances of exceptionally high risk of exposure to plague.

CONCLUSION

Plague is an acute bacterial illness that is typically transmitted to humans by the bites of infectious fleas, direct contact with infected animals, or inhalation of infectious respiratory droplets. In most instances, plague can be prevented by using an appropriate combination of a) personal protective measures; b) applications of insecticides to home, recreational, and work environments when plague has been detected in local animal or flea populations; c) insecticidal treatment of pets; d) avoidance of sick or dead animals; e) environmental modifications to reduce the amount of food and shelter available to rodents; and f) prophylactic antibiotic therapy for persons who are presumed to have been exposed to infection.

Although various modifications of killed plague vaccine have been available since World War II, its efficacy in protecting humans has not been adequately demonstrated. Pneumonic plague has developed in at least two persons despite vaccination, indicating that the vaccine may not be effective in the prevention of infection via inhalation of infectious respiratory droplets or other airborne materials. However, indirect evidence indicates that plague vaccine is effective for preventing flea-borne transmission of disease. Thus, plague vaccine is recommended for laboratory personnel who routinely are exposed to viable *Y. pestis*. Vaccine also should be considered for persons who regularly have contact with the wild-rodent hosts of plague or their fleas in areas where plague is enzootic or epizootic.

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