and in retrospectively reviewed cases in the United States. In view of streptomycin's adverse-reaction profile and limited availability, some experts now recommend gentamicin over streptomycin. In 2012, the FDA approved levofloxacin for prophylaxis and treatment of plague (including septicemic and pneumonic disease), making it the first antibiotic approved for a new indication under a regulatory approach based on animal studies alone, known as the Animal Rule. An FDA decision on ciprofloxacin is pending. Levofloxacin is more efficacious than ciprofloxacin for postexposure prophylaxis of inhalational anthrax in animal models and also received FDA approval for this indication (Chap. 261e); thus it is approved for multiagent prophylaxis in possible bioterrorism exposures.

While systemic chloramphenicol therapy is available in the resource-poor countries primarily affected by plague, it is less likely to be available or used in high-income countries because of its adverse effect profile. Tetracyclines are also effective and can be given by mouth but are not recommended for children under the age of 7 years because of tooth discoloration. Doxycycline is the tetracycline of choice; at an oral dosage of 100 mg twice daily, this drug was as effective as IM gentamicin (2.5 mg/kg twice daily) in a trial in Tanzania.

Although *Y. pestis* is sensitive to β-lactam drugs in vitro and these drugs have been efficacious against plague in some animal models, the response to penicillins has been poor in some clinical cases; thus β-lactams and macrolides are not generally recommended as first-line therapy. Chloramphenicol, alone or in combination, is recommended for some focal complications of plague (e.g., meningitis, endophthalmitis, myocarditis) because of its tissue penetration properties. Fluoroquinolones, effective in vitro and in animal models, are recommended in guidelines for possible bioterrorism-associated pneumonic plague and are increasingly used in therapy, although the only human efficacy data available so far are from a case report. Animal and in vitro studies suggest that fluoroquinolones other than levofloxacin, at doses used in systemic gram-negative sepsis, should be effective as therapy for plague: e.g., ciprofloxacin (400 mg twice daily IV, 500 mg twice daily by mouth), ofloxacin (400 mg twice daily IV or by mouth), or moxifloxacin (400 mg/d IV or by mouth).

PREVENTION

In endemic areas, the control of plague in humans is based on reduction of the likelihood of being bitten by infected fleas or exposed to infected droplets from either humans or animals with plague pneumonia. In the United States, residence and outdoor activity in rural areas of western states where epizootics occur are the main risk factors for infection. To assess potential risks to humans in specific areas, surveillance for *Y. pestis* infection among animal plague hosts and vectors is carried out regularly as well as in response to observed animal die-offs. Personal protective measures include avoidance of areas where a plague epizootic has been identified and publicized (e.g., by warning signs or closure of campsites). Sick or dead animals should not be handled by the general public. Hunters and zoologists should wear gloves when handling wild-animal carcasses in endemic areas. General measures to avoid rodent fleabite during outdoor activity are appropriate and include the use of insect repellant, insecticide, and protective clothing. General measures to reduce peridomestic and occupational human contact with rodents are advised and include rodent-proofing of buildings and food-waste stores and removal of potential rodent habitats (e.g., woodpiles and junk heaps). Flea control by insecticide treatment of wild rodents is an effective means of minimizing human contact with plague if an epizootic is identified in an area close to human habitation. Any attempt to reduce rodent numbers must be preceded by flea suppression to reduce the migration of infected fleas to human hosts. An oral F1-V subunit vaccine using raccoon poxvirus (RCN) as a vector protects prairie dogs against *Y. pestis* injections and is being investigated for efficacy in preventing disease in wild animals, thus potentially reducing human exposure.

Patients in whom pneumonic plague is suspected should be managed in isolation, with droplet precautions observed until pneumonia is excluded or effective antimicrobial therapy has been given for 48 h. Review of the literature published before the advent of antimicrobial agents suggests that the main infective risk is posed by patients in the final stages of disease who are coughing up sputum with plentiful visible blood and/or pus. Cotton and gauze masks were protective in these circumstances. Current surgical masks capable of barrier protection against droplets, including large respiratory particles, are considered protective; a particulate respirator (e.g., N95 or greater) is not required.

Antimicrobial Prophylaxis Postexposure antimicrobial prophylaxis lasting 7 days is recommended following household, hospital, or other close contact with persons with untreated pneumonic plague. (*Close contact* is defined as contact with a patient at <2 m.) In animal aerosol-infection studies, levofloxacin and ciprofloxacin are associated with higher survival rates than doxycycline (Table 196-3).

Immunization Studies with candidate plague vaccines in animal models show that neutralizing antibody provides protection against exposure but that cell-mediated immunity is critical for protection and clearance of *Y. pestis* from the host. A killed whole-cell vaccine used in humans required multiple doses, caused significant local and systemic reactions, and was not protective against pneumonic plague; this vaccine is not currently available in the United States. A live attenuated vaccine based on strain EV76 is still used in countries of the former Soviet Union but has significant side effects. The vaccines closest to licensure are subunit vaccines comprising recombinant F1 (rF1) and various recombinant V (rV) proteins produced in *Escherichia coli*, which are combined either as a fusion protein or as a mixture, purified, and adsorbed to aluminum hydroxide for injection. This combination protects mice and various nonhuman primates in laboratory models of bubonic and pneumonic plague and has been evaluated in phase 2 clinical trials. Special ethical considerations with controlled clinical studies involving plague in humans make prelicensure field efficacy studies unlikely. In the United States, the FDA is therefore prepared to assess plague vaccines for human use under the Animal Rule, using efficacy data and other results from animal studies as well as antibodies and other correlates of immunity from human vaccine recipients *(www.fda.gov/BiologicsBloodVaccines/ScienceResearch/BiologicsResearchAreas/ucm127288.htm)*. Live attenuated

TABLE 196-3 GUIDELINES FOR PLAGUE PROPHYLAXIS

Drug	Daily Dose	Interval, h	Route
Doxycycline			
Adult	200 mg	12 or 24	PO
Child ≥8 y	If ≥45 kg, give adult dosage; if <45 kg, give 2.2 mg/kg PO bid (maximum, 200 mg)	12	PO
Tetracycline			
Adult	1–2 g	6 or 12	PO
Child ≥8 y	25–50 mg/kg	6 or 12	PO
Levofloxacin			
Adult and child >50 kg	500 mg	24	PO
Child <50 kg and ≥6 months	8 mg/kg (not to exceed 250 mg/dose)	12	PO
Ciprofloxacin			
Adult	1 g	12	PO
Child	40 mg/kg	12	PO
Trimethoprim-Sulfamethoxazole			
Adult	320 mg	12	PO
Child	40 mg/kg	12	PO

Source: Dennis DT, Campbell GL: Plague and other *Yersinia* infections, in AS Fauci et al (eds): *Harrison's Principles of Internal Medicine.* 2008, p. 980; Inglesby TV et al: Plague as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. JAMA 283:2281, 2000; and FDA Drug Product Label Reference ID 3123374 *(www.accessdata.fda.gov/drugsatfda_docs/label/2012/020634s061,020635s067,021721s028lbl.pdf)*.