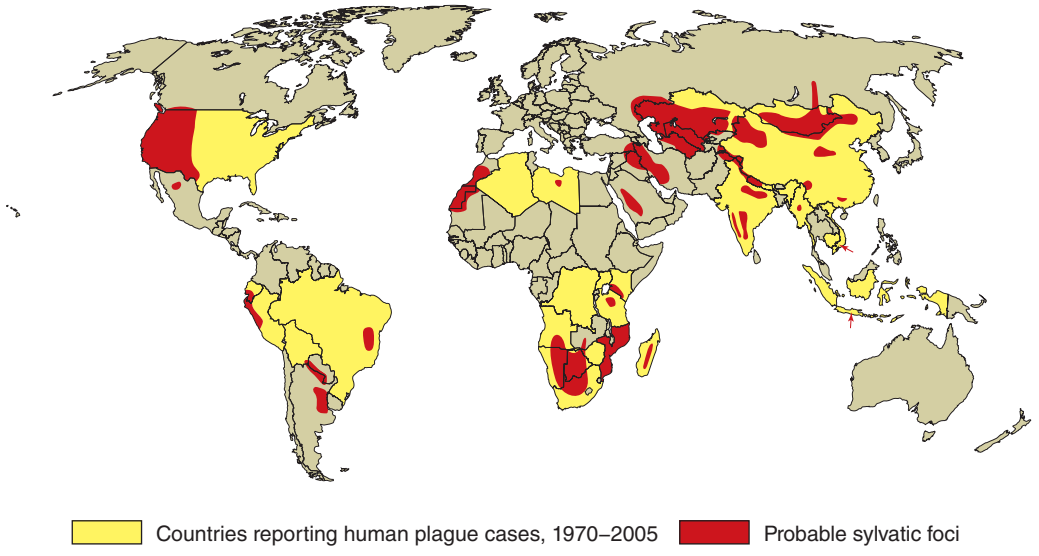

FIGURE 196-1 Approximate global distribution of *Yersinia pestis*. *(Compiled from WHO, CDC, and country sources. Reprinted with permission from DT Dennis, GL Campbell: Plague and other Yersinia infections, in Harrison's Principles of Internal Medicine, 17th ed, AS Fauci et al [eds]. New York, McGraw-Hill, Chap. 152, 2008.)*

Plague was introduced into North America via the port of San Francisco in 1900 as part of the Third Pandemic, which spread around the world from Hong Kong. The disease is presently enzootic on the western side of the continent from southwestern Canada to Mexico. Most human cases in the United States occur in two regions: "Four Corners" (the junction point of New Mexico, Arizona, Colorado, and Utah), especially northern New Mexico, northern Arizona, and southern Colorado; and further west in California, southern Oregon, and western Nevada (*http://www.cdc.gov/plague/maps/index.html*). From 1990 to 2011, 151 cases of plague were reported in the United States, a mean of seven cases per year. Most cases occurred from May to October—the time of year when people are outdoors and rodents and their fleas are most plentiful. The infection is most often acquired by fleabite in peridomestic environments; it can also be acquired through the handling of living or dead small mammals (e.g., rabbits, hares, and prairie dogs) or wild carnivores (e.g., wildcats, coyotes, or mountain lions). Dogs and cats may bring plague-infected fleas into the home, and infected cats may transmit plague directly to humans by the respiratory route. The last recorded case of person-to-person transmission in the United States occurred in 1925.

Plague most often develops in areas with poor sanitary conditions and infestations of rats—in particular, the widely distributed roof rat *Rattus rattus* and the brown rat *Rattus norvegicus* (which serves as a laboratory model of plague). Rat control in warehouses and shipping facilities has been recognized as important in preventing the spread of plague since the early twentieth century and features in the current WHO International Health Regulations. Urban rodents acquire infection from wild rodents, and the proximity of the former to humans increases the risk of transmission. The oriental rat flea *Xenopsylla cheopis* is the most efficient vector for transmission of plague among rats and onward to humans in Asia, Africa, and South America.

Worldwide, bubonic plague is the predominant form reported (80–95% of suspected cases), with mortality rates of 10–20%. The mortality rate is higher (22%) in the small proportion of patients (10–20%) with primary septicemic plague (i.e., systemic *Y. pestis* sepsis with no bubo; see "Clinical Manifestations," below) and is highest with primary pulmonary plague; in this, the least common of the main plague presentations, the mortality rate approaches 100% without antimicrobial treatment and is >50% even with such treatment. Rare outbreaks of pharyngeal plague following consumption of raw or undercooked camel or goat meat have been reported.

A total of 81 (76%) of the 107 plague cases reported in the United States from 1990 to 2005 were primary bubonic disease, 19 (18%) were primary septicemic disease, and 5 (5%) were primary pneumonic disease; 2 cases (2%) were not classified. Eleven cases (10%) were fatal.

PATHOGENESIS

As mentioned earlier, genetic evidence suggests that *Y. pestis* is a clone derived from the enteric pathogen *Y. pseudotuberculosis* in the recent evolutionary past (9000–40,000 years ago). The change from infection by the fecal-oral route to a two-stage life cycle, with alternate parasitization of arthropod and mammalian hosts, followed the acquisition of two plasmids (pFra and pPst) and the inactivation of remarkably few *Y. pseudotuberculosis* genes in conjunction with preexisting properties of the *Y. pseudotuberculosis* ancestor (e.g., the presence of a third plasmid, pYV, and the capacity to cause septicemia). In the arthropod-parasitizing portion of its life cycle, *Y. pestis* multiplies and forms biofilm-embedded aggregates in the flea midgut after ingestion of a blood meal containing bacteria. In some fleas, biofilm-embedded bacteria eventually fill the proventriculus (a valve connecting the esophagus to the midgut) and block normal blood feeding. Both "blocked" fleas and those containing masses of biofilm-embedded *Y. pestis* without complete blockage inoculate *Y. pestis* into each bite site. The ability of *Y. pestis* to colonize and multiply in the flea requires phospholipase D encoded by the *ymt* gene on the pFra plasmid, and biofilm synthesis requires the chromosomal *hms* locus shared with *Y. pseudotuberculosis*. However, three *Y. pseudotuberculosis* genes inhibiting biofilm formation or promoting its degradation are inactivated in *Y. pestis*, together with urease, which causes acute flea gastrointestinal toxicity. Blockage takes days or weeks to come about after initial infection of the flea and is followed by the flea's death. In addition, many flea vectors (including *X. cheopis*) are able to transmit plague in an early-phase unblocked state for up to 1 week after feeding, but 10 fleas in this state are required to infect a mammalian host (mass transmission).

Y. pestis disseminates from the site of inoculation in the mammalian host in a process initially dependent on plasminogen activator Pla, which is encoded by the small pPst plasmid. This surface protease activates mammalian plasminogen, degrades complement, and adheres to the extracellular matrix component laminin. Pla is essential for the high-level virulence of *Y. pestis* in mice by subcutaneous or intradermal injection (laboratory proxies for fleabites) and for the development of primary pneumonic plague. When actual fleabite inoculation is used in mouse models, the fimbrial capsule-forming protein (Ca1 or fraction 1; F1 antigen) encoded on pFra increases the efficiency of transmission, and plasminogen activator is required for the formation