Y. pseudotuberculosis and *Salmonella* strains expressing *Y. pestis*–specific antigens have been shown to be protective in laboratory animal models of bubonic and pneumonic plague and could be delivered by the oral route. A wide variety of other delivery mechanisms for *Y. pestis* antigens are being explored. Antigens other than F1 and V that could be added to subunit vaccines are being investigated. Advances providing impetus for exploration of these antigens are (1) the recovery of F1-negative *Y. pestis* strains from natural sources and (2) the observation that F1 antigen is not required for virulence in primate models of pneumonic plague.

YERSINIOSIS

Yersiniosis is a zoonotic infection with an enteropathogenic *Yersinia* species, usually *Yersinia enterocolitica* or *Y. pseudotuberculosis*. The usual hosts for these organisms are pigs and other wild and domestic animals; humans are usually infected by the oral route, and outbreaks from contaminated food occur. Yersiniosis is most common in childhood and in colder climates. Patients present with abdominal pain and sometimes with diarrhea (which may not occur in up to 50% of cases). *Y. enterocolitica* is more closely associated with terminal ileitis and *Y. pseudotuberculosis* with mesenteric adenitis, but both organisms may cause mesenteric adenitis and symptoms of abdominal pain and tenderness that result in pseudoappendicitis, with the surgical removal of a normal appendix. Diagnosis is based on culture of the organism or convalescent serology. *Y. pseudotuberculosis* and some rarer strains of *Y. enterocolitica* are especially likely to cause systemic infection, which is also particularly common among patients with diabetes or iron overload. Systemic sepsis is treatable with antimicrobial agents, but postinfective arthropathy responds poorly to such therapy. Fourteen other *Yersinia* species are now recognized, but all lack the virulence plasmid pYV common to *Y. pestis, Y. pseudotuberculosis*, and *Y. enterocolitica* and are generally considered to be, at most, opportunistic pathogens of humans (*Y. aldovae, Y. aleksiciae, Y. bercovieri*, *Y. entomophaga*, *Y. frederiksenii, Y. intermedia, Y. kristensenii, Y. massiliensis, Y. mollaretii, Y. nurmii, Y. pekkanenii, Y. rohdei, Y. similis*, and *Y. ruckeri*). Molecular phylogeny shows that *Y. enterocolitica* is more distantly related to *Y. pseudotuberculosis* than these other *Yersinia* species, and the similar virulence plasmid they share has probably been acquired independently by at least one of the two since the species diverged.

EPIDEMIOLOGY

Y. enterocolitica *Y. enterocolitica* is found worldwide and has been isolated from a wide variety of wild and domestic animals and environmental samples, including samples of food and water. In vitro, *Y. enterocolitica* is resistant to predation by the protozoon *Acanthamoeba castellanii* and can survive inside it, suggesting a possible mode of environmental persistence. Strains are differentiated by combined biochemical reactions (biovar) and serogroup. Most clinical infections are associated with serogroups O:3, O:9, and O:5,27, with a declining number of O:8 infections in North America. Some O:8 infections, previously confined to North America, have been reported from Europe and Japan in recent years, and serogroup O:8 now causes a high percentage of yersiniosis cases in Poland. Yersiniosis, mostly due to *Y. enterocolitica*, is the third commonest zoonosis reported in Europe; most reports come from northern Europe, especially Germany and Scandinavia. The incidence is highest among children; children under the age of 4 years are more likely to present with diarrhea than are older children. Abdominal pain with mesenteric adenitis and terminal ileitis is more prominent among older children and adults. Septicemia is more likely in patients with preexisting conditions such as diabetes mellitus, liver disease, any condition involving iron overload (including thalassemia and hemochromatosis), advanced age, malignancy, or HIV/AIDS. As in enteritis of other bacterial etiologies, postinfective complications such as reactive arthritis occur mainly in individuals who are HLA-B27 positive. Erythema nodosum (see Fig. 25e-40) following *Yersinia* infection is not associated with HLA-B27 and is more common among women than among men.

Consumption or preparation of raw pork products (such as chitterlings) and some processed pork products is strongly linked with infection because a high percentage of pigs carry pathogenic *Y. enterocolitica* strains. Outbreaks of *Y. enterocolitica* infection have been associated with consumption of milk (pasteurized, unpasteurized, and chocolate-flavored) and various foods contaminated with springwater. Person-to-person transmission is suspected in a few cases (e.g., in nosocomial and familial outbreaks) but is much less likely with *Y. enterocolitica* than with other causes of gastrointestinal infection, such as *Salmonella*. A multivariate analysis indicates that contact with companion animals is a risk factor for *Y. enterocolitica* infection among children in Sweden, and low-level colonization of dogs and cats with *Y. enterocolitica* has been reported. Transfusion-associated septicemia due to *Y. enterocolitica*, while recognized as a very rare but frequently fatal event for over 30 years, has been difficult to eradicate.

Y. pseudotuberculosis *Y. pseudotuberculosis* is less frequently reported as a cause of human disease than *Y. enterocolitica*, and infection with *Y. pseudotuberculosis* is more likely to present as fever and abdominal pain due to mesenteric lymphadenitis. This organism is associated with wild mammals (rodents, rabbits, and deer), birds, and domestic pigs. Strains are differentiated by combined biochemical reactions (biovar) and serogroup. Although outbreaks are generally rare, several have recently occurred in Finland in association with consumption of lettuce and raw carrots.

PATHOGENESIS

The usual route of infection is oral. Studies with both *Y. enterocolitica* and *Y. pseudotuberculosis* in animal models suggest that initial replication in the small intestine is followed by invasion of Peyer's patches of the distal ileum via M cells, with onward spread to mesenteric lymph nodes. The liver and spleen can also be involved after oral infection. The characteristic histologic appearance of enteropathogenic yersiniae after invasion of host tissues is as extracellular microabscesses surrounded by an epithelioid granulomatous lesion.

Experiments involving oral infection of mice with tagged *Y. enterocolitica* show that only a very small proportion of bacteria in the gut invade tissues. Individual bacterial clones from an orally inoculated pool give rise to each microabscess in a Peyer's patch, and the host restricts the invasion of previously infected Peyer's patches. A prior model positing progressive bacterial spread from Peyer's patches and mesenteric lymph nodes to the liver and spleen appears to be inaccurate: spread of individually tagged clones of *Y. pseudotuberculosis* to the liver and spleen of mice occurs independently of regional lymph node colonization and in mice lacking Peyer's patches.

Invasion requires the expression of several nonfimbrial adhesins, such as invasin (Inv) and—in *Y. pseudotuberculosis*—*Yersinia* adhesin A (YadA). Inv interacts directly with β1 integrins, which are expressed on the apical surfaces of M cells but not enterocytes. YadA of *Y. pseudotuberculosis* interacts with extracellular matrix proteins such as collagen and fibronectin to facilitate host cell integrin association and invasion. YadA of *Y. enterocolitica* lacks a crucial N-terminal region and binds collagen and laminin but not fibronectin and does not cause invasion. Inv is chromosomally encoded, whereas YadA is encoded on the virulence plasmid pYV. YadA helps to confer serum resistance by binding host complement regulators such as factor H and C4-binding protein. Another chromosomal gene, *ail* (attachment and invasion locus), encodes the extracellular protein Ail, which also confers serum resistance by binding these complement regulators.

By binding to host cell surfaces, YadA allows targeting of immune effector cells by the pYV plasmid–encoded type III secretion system (*injectisome*). As a consequence, the host's innate immune response is altered; toxins (*Yersinia* outer proteins, or Yops) are injected into host macrophages, neutrophils, and dendritic cells, affecting signal transduction pathways, resulting in reduced phagocytosis and inhibited production of reactive oxygen species by neutrophils, and triggering apoptosis of macrophages. Other factors functional in invasive disease include yersiniabactin (Ybt), a siderophore produced by some strains of *Y. pseudotuberculosis* and *Y. enterocolitica* as well as other Enterobacteriaceae. Yersiniabactin allows bacteria to access iron from saturated lactoferrin during infection and reduces the production of reactive oxygen species by innate immune effector cells, thereby