Bubonic plague infections begin in the dermis when the pathogen is introduced by a flea during a routine blood feed. Several barriers separate *Yersinia pestis* from its replicative niche, including phagocytic cells in the dermis and the refractory midgut environment of the vector. For this flea-borne disease, very little is known about the genetic factors that influence the establishment of infection in the flea midgut, the mechanism of transmission to naive hosts, trafficking of bacteria to the mammalian lymph node, or survival in disparate environments. Despite its lethality and the discovery of antibiotic resistant isolates, no licensed plague vaccine has been developed for use in the U.S. or Western Europe. Even a single cell of *Y. pestis* can initiate a lethal case of bubonic plague. Modern pandemics have originated from the endemic maintenance of flea and rodent interactions, as such, an improved understanding of genetic determinants that contribute to *Y. pestis* persistence, virulence, and transmission is warranted. In order to achieve this goal, we have generated improved genetic tools for studying mammalian pathogenesis of bubonic plague. In addition, we have developed and improved multiple model systems for comprehensive studies of the *Yersinia pestis* life cycle. Furthermore, we identified bacterial genetic factors that influenced survival and virulence in both mammalian and insect hosts. Ideally, the data provided will allow researchers to acquire consistent and reliable data about the *Y. pestis* life cycle that may ultimately improve epidemiological modeling and prevention of disease. Holistic and comprehensive research directed at the host-vector-pathogen interface will likely lead to development of methods for controlling vector-borne pathogens, like *Yersinia pestis*. 