Review Article

Pathogenesis of *Y. enterocolitica* and *Y. pseudotuberculosis* in Human Yersiniosis

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Yersiniosis is a food-borne illness that has become more prevalent in recent years due to human transmission via the fecal-oral route and prevalence in farm animals. Yersiniosis is primarily caused by *Yersinia enterocolitica* and less frequently by *Yersinia pseudotuberculosis*. Infection is usually characterized by a self-limiting acute infection beginning in the intestine and spreading to the mesenteric lymph nodes. However, more serious infections and chronic conditions can also occur, particularly in immunocompromised individuals. *Y. enterocolitica* and *Y. pseudotuberculosis* are both heterogeneous organisms that vary considerably in their degrees of pathogenicity, although some generalizations can be ascribed to pathogenic variants. Adhesion molecules and a type III secretion system are critical for the establishment and progression of infection. Additionally, host innate and adaptive immune responses are both required for yersiniae clearance. Despite the ubiquity of enteric *Yersinia* species and their association as important causes of food poisoning world-wide, few national enteric pathogen surveillance programs include the yersiniae as notifiable pathogens. Moreover, no standard exists whereby identification and reporting systems can be effectively compared and global trends developed. This review discusses yersinial virulence factors, mechanisms of infection, and host responses in addition to the current state of surveillance, detection, and prevention of yersiniosis.

1. Introduction

Yersiniosis is typically a self-limiting, gastrointestinal disease of global concern. However, despite the known association of the causative agents (*Y. enterocolitica*, YE, and very rarely *Y. pseudotuberculosis*, YPT) with both gastroenteritis and extraintestinal infections, it remains a poorly understood disease. Sporadic cases are still reported in which food is not suspected as the source of infection, and isolation from contaminated food sources is often problematic. Because yersiniosis is considered relatively uncommon and YE and YPT are ubiquitous, food and water supplies are not regularly monitored for these bacterial pathogens. However, the ability of the yersiniae to persist in a nonculturable but viable state in natural samples [1] and to grow and thrive at refrigeration temperatures ($\sim$4°C) suggests that their contribution to disease might be underappreciated.

1.1. YE Infections.

The major causative agent of yersiniosis is the gram-negative, zoonotic bacterial pathogen, YE, which is typically transmitted via the fecal-oral route [2]. The closely related YPT can also cause yersiniosis, but human YPT infections are less frequent than those caused by YE. Yersiniosis has been observed on all continents [3] but is most common in European countries. Some of the challenges associated with linking yersiniosis to its source of contamination are attributable to the heterogeneity of yersiniae populations within a plethora of environments and reservoirs including: soil, water, and a variety of animals.

Yersiniosis is an important infection in European brown hares [4] and has additionally been detected in Canadian beavers, snowshoe hares, and muskrats [5]. Additionally, YE and YPT have been isolated form bats in Germany [6]. More relevant to humans is the prevalence of the yersiniae in animal food sources, particularly pigs and pork products [7–9], and more recently in domestic farm dogs in China [10]. Further complicating the picture of disease transmission, a recent study found that wild rodents on a European pig farm tested positive for YE, suggesting that rodents might serve as interspecies carriers between reservoirs [11]. YE has also been isolated from flies found in farm piggeries and kitchens [12], suggesting that arthropod vectors/insects might play a role in the transmission of the enteric yersiniae between animals and humans. Flies might also facilitate the spread of nosocomial infections which is of particular concern because there is at least one report of flies in Libyan hospitals carrying antibiotic-resistant strains of bacteria belonging to the *Enterobacteriaceae* family [13]. The major source of yersiniosis is swine, but recent isolates from contaminated chicken, milk, tofu, and water have also been reported [8, 14].

In healthy, immunocompetent individuals, yersiniosis symptoms range from mild, self-limiting diarrhea to mesenteric lymphadenitis. However, in immunocompromised individuals chronic conditions such as reactive arthritis have also been observed [15]. YE infection is generally established via digestion of contaminated food or water followed by bacterial adherence to small intestinal epithelial cells and eventual crossing of the intestinal barrier *via* M cells [16]. Subsequently, YE bacilli replicate in Peyer's patches and can sometimes spread to more distant lymphoid tissues, such as the mesenteric lymph nodes [16–18]. Dissemination from the distal ileum to the spleen and liver is relatively common, followed by extracellular replication and formation of monoclonal microabscesses [19]. The most common infection is acute gastroenteritis, mainly observed in children and infants on account of being somewhat immunocompromised due to an immature immune system. However, a host of other infections and complications can also occur in older children and adults, including pseudoappendicular syndrome, mycotic aneurysms [20–28], and, more rarely, sepsis as a secondary complication of yersiniosis or from blood transfusions. Several chronic conditions have also been described including: reactive arthritis, erythema nodosum, uveitis, glomerulonephritis, and myocarditis [3, 29]. While enteropathogenic yersiniosis is typically self-limiting in healthy individuals, the mortality rate can reach as high as 50% in immunocompromised persons, as a result of systemic bacterial dissemination [30].

1.2. YPT Infections. YPT causes zoonotic infections in a variety of hosts, including both wild and domestic animals and birds [31]. Human YPT infections, though less common than those caused by YE, are most often acquired from contaminated food or water [32]. Clinically, YPT infections typically present as abscess-forming mesenteric lymphadenitis and diarrhea but can also lead to secondary complications, such as perforation [33], subacute obstruction syndrome [34], intussusceptions [35], and acute renal failure [36] in

rare cases. Additionally, patients with severe gastrointestinal bleeding in cases of YPT colitis have also been reported [37–39]. Similar to YE, the most common features of YPT infections in humans are ileocolitis and mesenteric lymphadenitis [40], the latter of which can affect appendix tissue and be mistaken for appendicitis [41]. YPT infections can be acute or chronic [42], with reticulogranulocytic infiltration, enlarged follicles, and necrosis with abscess formation in mesenteric lymph nodes [39, 43, 44]. Infection is usually self-limiting, but rare cases of sepsis can lead to a very high mortality rate (>75%) [45]. In addition to appendicitis, YPT infections have been confused with tumoral lesions [46], terminal ileitis, and Crohn's disease [47]. YPT has also been implicated in reactive arthritis, erythema nodosum, and Kwasaki autoimmune syndrome [48].

1.3. YE Epidemiology. Surveillance of human YPT infections is not routinely performed, and there are thus no complete databases from which information can be used to gauge trends in human YPT infections. However, there are several national surveillance networks that include yersiniosis in weekly, monthly, and yearly reports of human enteric disease cases/isolations, particularly those collected by member states of the European Union, the United States, and New Zealand. Potential sources of epidemiological data include clinical reports, laboratory isolations, sentinel site studies, reported cases, and rates calculated as cases per 100,000 persons in the affected population surveillance area per annum. Differences in reporting methods, isolation methods, and availability of strain information greatly complicate comparisons among countries and sometimes even among different regions/states/territories within an individual country. Furthermore, yersiniosis is infrequently monitored in developing countries, where enteric diseases are a major cause of infant and child mortality. For instance, the World Health Organization initiated a plan to address this issue in Africa in 1998 by working with member states and technical partners to implement the integrated disease surveillance and response (IDSR) program, but yersiniosis is not included as a primary surveillance target. Similarly, the Medical Sciences Center for Disease Control (http://www.moh.gov.cn), a division of China's Ministry of Health, reports communicable disease incidences on a weekly basis, but the plague is the only yersiniae-associated disease included in their surveillance efforts.

Despite the lack of surveillance in many countries, including Africa, Asia, the Middle East, Pacific Islands, Latin America, the Caribbean, and others, there are several national agencies in North America and Europe that provide yearly reports which include sporadic yersiniosis cases, outbreaks, and incidence rates in both humans and animals. As shown in Figure 1, there was a broad range of case reports for North America (including the US and Canada), Oceania (including Australia and New Zealand), and several European countries. For instance, Ireland reported between 3 and 14 isolations of YE/YPT from humans between the years of 2000 and 2009, while Germany reported between 3,906 and 7,186 confirmed cases of human yersiniosis during this same time
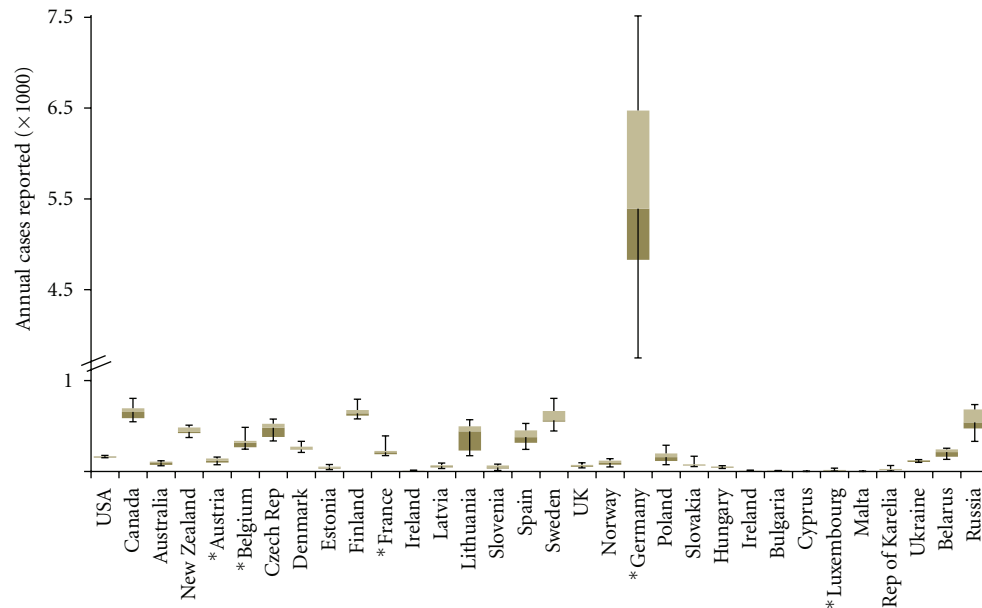
FIGURE 1: Human yersiniosis cases reported for selected countries that conduct active annual surveillance for the yersiniae. Surveillance data for years 2000 to 2009 were collected from national repositories for Canada (National Microbiology Laboratory, http://www .publichealth.gc.ca), the United States (FoodNet, http://www.cdc.gov/foodnet), 24 European Union members (European Food Safety Authority, http://www.efsa.europa.eu), New Zealand (The Institute of Environmental Science and Research, http://www.surv.esr.cri.nz), Australia (OZFoodNet, http://www.ozfoodnet.gov.au), Northwestern Russia, the Republic of Karelia, Ukraine, and Belarus (EpiNorth Project, http://www.ozfoodnet.gov.au). Russian data was obtained only from the following participating regions: Arkhangelsk oblast, Kaliningrad oblast, Leningrad oblast, Murmansk oblast, Nenets Autonomous okrug, Novgorod oblast, Pskov oblast, St. Petersburg City, Vologda oblast, and the Republic of Komi. For comparison, countries defined as Western European nations based on the classification scheme used by the United Nations include Austria, Belgium, France, Germany, and Luxembourg (which are marked with an asterisk). As shown, Germany reported the greatest number of human cases per annum for the ten-year period included (years 2000–2009), compared to all other countries examined, including the bordering countries of Denmark, Poland, Czech Republic, Austria, and France. The annual cases reported are shown on the *ordinate*, with the axis broken between 1,000 and 4,500 cases to allow the inclusion of Germany and other countries in one graphical display. Yearly cases were not adjusted for population differences. Individual countries are listed on the *abscissa*. USA: United States; UK: United Kingdom.

period (Figure 1). Although, incidences have declined over the last 10 years (Figure 2), German yersiniosis cases account for more than half of all reported European yersiniosis events and ~90% of those within Western European nations that regularly surveyed their populations for YE-associated infections during the aforementioned ten-year-time frame (Figure 1). The reasons for the dramatically higher yersiniosis incidence rate in Germany compared to all other countries with active YE/YPT surveillance programs is unclear, but potential factors include variability in yersiniae isolation procedures and reporting systems, differences in clinical diagnostic frequency, degree of underreporting, prevalence of YE and YPT in animal reservoirs, differences in food processing, and variability in the consumption of meat products. There is some evidence to support the idea that higher meat consumption, particularly pork in Germany compared to other European nations might correlate with Germany's higher incidence of yersiniosis [49].

1.4. YE Genomics. YE is a heterogeneous group of organisms characterized by six biotypes and 60 serotypes. Biotypes can be distinguished based on level of pathogenicity, only one of which is nonpathogenic (Biotype 1A). "Old World" YE

includes Biotypes 2–5, which are weakly pathogenic. Most virulent is the "New World" Biotype 1B, which is highly pathogenic to humans and lethal in a mouse model of infection [50]. Of the sixty serotypes of YE, only eleven have been associated with disease in humans, and the majority can be traced to only three commonly virulent serotypes: O:3, O:8, and O:9. These three serotypes are generally considered the causative agents of yersiniosis and vary based on geography. For instance, strain 1B/O:8 has been the predominant version of pathogenic YE in the United States [15]; in contrast, strain 3/O:9 is the most common cause of yersiniosis in China and in Europe [51, 52].

Isolates from these two pathogenic strains were sequenced [53, 54] and recently compared to identify common and unique virulence regions [54]. The results of this analysis indicated that the two strains share considerable genetic conservation/similarity, including most of the known YE virulence determinants. However, several 1B/O:8 key virulence regions were absent in the 3/O:9 strain [54] including high pathogenicity island (HPI) [55], *Yersinia* type II secretion 1 (*yts1*) [56], and the *Yersinia* Type III secretion apparatus (*ysa*). Likewise, the 3/O:9 strain possessed pathogenicity regions absent in the highly pathogenic 1B/O:8 strain. Strain
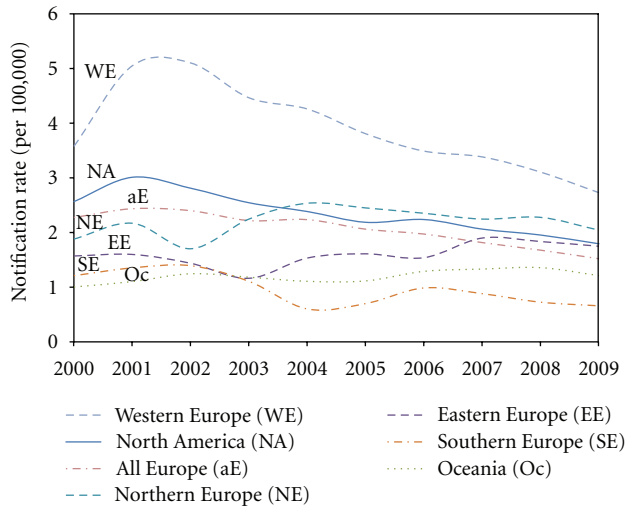
Figure 2: Line graph comparing the yearly incidence rate of yersiniosis reported for various European countries, North America, and Oceania. Surveillance data were collected from national repositories for Canada (National Microbiology Laboratory, http://www.publichealth.gc.ca), the United States (FoodNet, http://www.cdc.gov/foodnet), 24 European Union members (European Food Safety Authority, http://www.efsa.europa.eu), New Zealand (The Institute of Environmental Science and Research, http://www.surv.esr.cri.nz), Australia (OZFoodNet, http://www.ozfoodnet.gov.au), Northwestern Russia, the Republic of Karelia, Ukraine, and Belarus (EpiNorth Project, http://www.epinorth.org). The yearly incidence rate (cases per 100,000 in the surveillance population) was calculated based on total reported cases per year and published population figures included in published surveillance reports or governmental census sites. For countries where surveillance did not include the entire population, rates were adjusted based on the surveillance population and case information provided with the original surveillance data. For countries that did not provide data for all years included in the analysis (i.e., 2000–2009), the rate was extrapolated using linear regression (e.g., Canada, Australia, and Luxembourg). Notification rate (calculated as explained above) per 100,000 persons is shown on the *ordinate*, and a total of 30 countries presented by region are displayed on the *abscissa*. Western Europe (WE) includes Austria, Belgium, France, Germany, and Luxembourg. North America includes Canada and the United States. Northern Europe includes Latvia, Lithuania, Estonia, the United Kingdom, Ireland, Denmark, Norway, Finland, Sweden, and the Republic of Karelia. Eastern Europe includes the Czech Republic, Poland, Slovakia, Hungary, Bulgaria, the Ukraine, Belarus, and Northwestern Russia. Southern Europe includes Slovenia, Spain, and Malta. Oceania includes New Zealand and Australia. All of the available European data considered together (aE), representing a total of 28 countries, is also shown for comparison.

3/O:9-specific regions included a novel chromosomally encoded Type III secretion system (T3SS), ATP binding cassette transporter system, toxin-related gene clusters, and a flagellar gene cluster [54]. Sequencing additional YE strains, such as 4/O:3 that has recently emerged as an important cause of yersiniosis in the United States [57], will likely contribute to a better understanding of the relationship between strain-specific virulence factors and variations in clinical sequelae.

1.5. YPT Genomics. YPT can be classified into 14 distinct biotypes [58], five of which are almost exclusively pathogenic (O1–O5). The remaining nine biotypes (O6–O14) have been isolated from animals and the environment but never from human clinical samples [58–61]. Both pathogenic and non-pathogenic YPT can be further subdivided into 21 serotypes [62] based on the distribution of about 30 different O factors (O-specific polysaccharide of lipopolysaccharide [LPS]) within the species [58]. These serotypes vary geographically and in degree of pathogenicity [63], generally correlating with the size and presence of the chromosomal pathogenicity island, HPI [63]. Only Biotype O1 strains contain a complete, intact HPI. Biotype O3 contains a truncated version, and the pathogenicity island is entirely absent from all other YPT strains that have thus far been examined [64–66]. The pathogenicity of YPT depends on the presence of the T3SS-encoding virulence plasmid pYV [67], YPMa [68], and HPI [69] (described in detail in the next section), and clinical features are closely correlated with the various combinations of these three virulence factors. For instance, pYV is absent in one-fourth of the known virulent serotypes, which instead express the YPMa superantigen variant and/or HPI proteins [63]. The heterogeneous distribution of these factors accounts for the differences in clinical manifestations of infections in the Far East, Europe, and Western countries [63, 66, 70–72].

1.6. YE and YPT Virulence Factors. The genomes of YE, YPT, and YP are 97% identical, but the three bacteria cause vastly different diseases in humans, despite having a shared tropism for lymph nodes [73–76]. Their distributions of shared and unique virulence factors play a critical role in the different routes of infection, types of infections, and severity of disease in humans. Both chromosomal and plasmid-derived virulence factors play a role in yersiniae pathogenesis and in the establishment and progression of yersiniosis. YE pathogenicity depends on the presence of the 70-kb plasmid associated with *Yersinia* virulence, pYV [67, 77–79]. The pYV plasmid differentiates pathogenic from non-pathogenic strains, because it is essential for virulence [79]. The highly pathogenic *Y. enterocolitica* biotype 1B also harbors the chromosomal high-pathogenicity island (HPI), as do almost all European strains of *Y. pseudotuberculosis* serotype O1 [69]. HPI encodes proteins that are involved in the biosynthesis, regulation, and transport of the siderophore yersiniabactin [80, 81] and has thus been referred to as an "iron capture island" [63, 69]. There are five main genes within this island (*psn*, *irp1*, *irp2*, *ybtP*, and *ybtQ*) that are involved in the yersiniabactin system [80, 82, 83]. This system is positively regulated by YtbA, which is, itself, negatively regulated by the iron-responsive regulator Fur [84]. The *psn* and *irp2* genes are important for the high-pathogenicity phenotype of YPT [69, 85].

Almost all Far Eastern strains of YPT additionally produce one of three variants of a chromosomally encoded novel
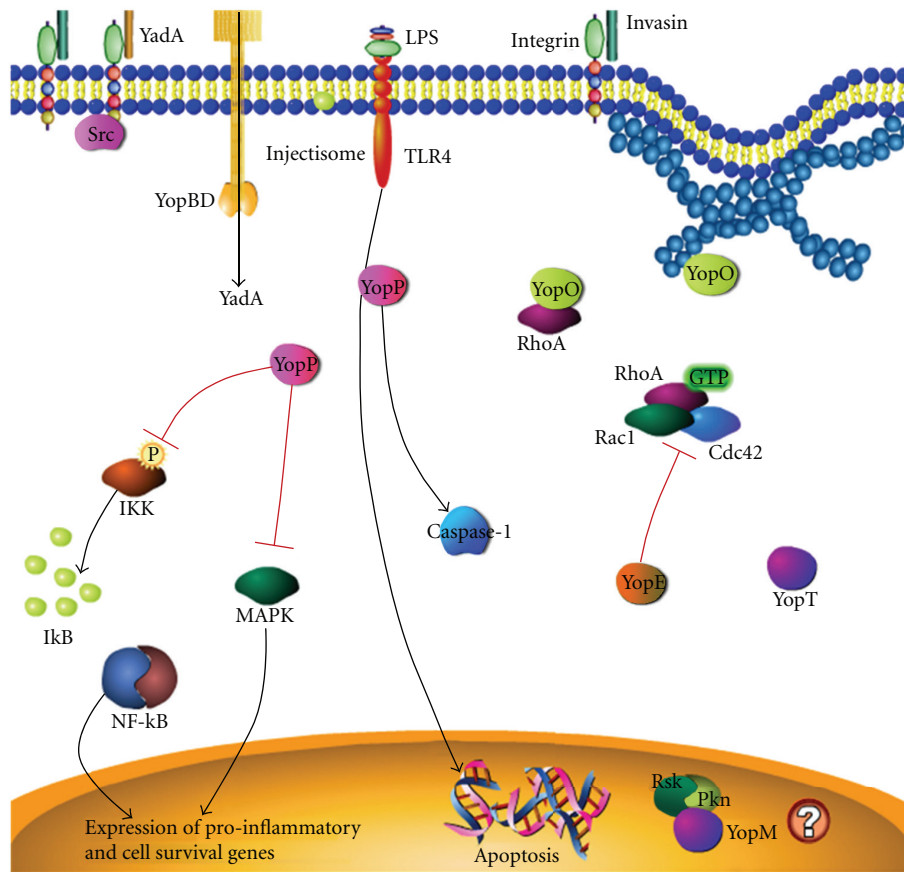
FIGURE 3: Mechanisms of action of the enteropathogenic yersiniae Ysc T3SS effectors (Yops) on host cell signaling and survival. As shown, membrane-bound *Yersinia* Yad and invasin proteins bind host cell β1-integrins, bringing the bacteria into close proximity to the host cell thereby facilitating insertion of the T3SS injectisome needle-like structure into the targeted host cell. Yops are then translocated across the host plasma membrane and into the cytoplasm, where they interact with the cytoskeleton and host cell signaling molecules. YopO/YpkA interacts directly with the cytoskeleton, as well as the small GTPase signaling molecules, RhoA, Rac1, and Cdc42. YopE inhibits the activities of RhoA, Rac1, and Cdc42. YopP/J promotes LPS-induced host cell apoptosis and directly induces capsase-1 cleavage. YopP/J also inhibits mitogen-activated protein kinases (MAPK) and IKK-mediated NF-κB activation, which prevents expression of proinflammatory and cell survival genes. YopM forms a complex with Rsk and Pkn in the host cell nucleus, which is believed to contribute to bacterial pathogenesis. The figure was produced using Pathway Builder 1.0, a cell signaling drawing tool provided through the Protein Lounge (http://www.ProteinLounge.com).

superantigenic toxin YPM (YPT-derived mitogen) encoded by the *ypm* gene [86, 87]. The original YPM (renamed YPMa) is encoded by *ypmA* [88] and plays a more important role in systemic infections than in gastroenteritis [68]. The other two variants, YPMb and YPMc, are encoded by the *ypmB* and *ypmC* genes, respectively [88, 89].

The small conserved RNA chaperone protein, Hfq is required for full virulence of a variety of pathogenic bacteria, including both YE and YPT [90]. Hfq is required for expression of the heat-stable enterotoxin Yst in YE [91]. In YPT, Hfq plays a role in the regulation of motility, intracellular survival, and production of T3SS effectors [90].

The YPT chromosomally encoded PhoP/Q system [92] regulates survival and growth in macrophages [93, 94] and covalent modifications of LPS that reduce its stimulatory capacity [95], thereby empowering bacteria to avoid, minimize, or delay macrophage activation. In a mouse model of intestinal infection, mutants devoid of PhoP were 100-fold attenuated in virulence due to a reduced capacity to survive and replicate intracellularly within macrophages [93]. The global PhoPQ regulon also senses the reduction in Mg^{2+} and possibly Mn^{2+} levels that characterizes the intracellular environment of host cells. MntH, a putative *Yersinia* Mn^{2+} transporter, was recently proposed to promote survival of the bacteria within phagocytic vacuoles by protecting them from reactive oxygen species [96].

1.7. Establishment of Yersiniosis Infection. In many pathogens, virulence factors are closely coupled to temperature, and this temperature regulation is particularly important for the establishment of infection. At environmental temperatures (less than 28°C) and under acidic conditions at 37°C, the enteric yersiniae optimally express the invasin protein, which is encoded by the chromosomal *inv* locus [17, 18]. Upon ingestion, invasin binds to B1 integrins on host cells and facilitates penetration of the epithelial layer (**Figure 3**).

The gradual increase in temperature within the host induces the expression of virulence factors necessary to establish a stronghold within the lymph tissues and evade immune system detection. Expression of the chromosomal *ail* (*attachment invasion*) *locus*, for instance, is induced at 37°C, and the resulting Ail/OmpX protein further enhances epithelial cell invasion. Establishment of infection also requires translocation of toxic effectors via a T3SS as well as "other transporter systems" [97]. Regulation of adherence and invasion is mediated via the regulator of virulence A (RovA), which positively regulates *inv* expression, *Yersinia*-modulating protein (YmoA), and histone-like nucleoid structuring protein (H-NS) [98–103].

Yersinia adhesion A protein (YadA) also mediates mucus and epithelial cell attachment and, in concert with invasin, promotes host cell invasion (Figure 3). YadA is a multifunctional, surface-exposed virulence factor encoded on the pYV virulence plasmid that confers the ability to adhere to extracellular matrix proteins [104–106]. Induction of YadA expression is coordinated with the upregulation of Yops (*Yersinia* outer membrane proteins) [107, 108]. The contribution of YadA to virulence is greater for YE than for YPT, playing a significant role in the positive regulation of both adherence to and invasion of host cells [105, 109]. YadA plays only a minor role in YPT, conferring merely an adhesive phenotype [110–112]. Similar to invasin, YadA initiates internalization by binding to extracellular fibronectin that is bound to a 5b1 integrin [105]. YadA from YPT and YE binds fibronectin, collagen I, II, and IV, and laminin, albeit with different affinities thus promoting variable virulence properties [105]. YadA elicits an inflammatory response in epithelial cells by inducing mitogen-activated protein kinase- (MAPK-) dependent interleukin (IL)-8 production and by contributing to the resulting intestinal inflammatory cascade [113, 114]. Interaction of YadA with collagen has been proposed to contribute to chronic yersiniosis infections, such as the development of reactive arthritis [113–116] which has been demonstrated in a rat model [117–119].

In addition to inhibition and invasion of host cells, both Ail and YadA play significant roles in complement resistance and immune evasion. Ail and YadA inhibit the alternative complement pathway by binding regulator factor H and usurping its natural function to prevent lysis of host cells [120–123]. Ail and YadA similarly subvert the classical complement and lectin pathways by binding to C4b-binding protein, thereby promoting the degradation of the C4b complement factor and preventing the formation of the C3 convertase that would otherwise lead to lysis of the bacterial cells [123].

Other YPT virulence factors include the putative DNA adenine methyltransferase, YamA, which is required for full virulence [124], and several proteins that aid in bacterial survival under acidic conditions. An aspartate-dependent acid survival system was recently described for YPT, which plays a role in bacterial survival and thus facilitates establishment of infection [125]. A drop in pH induces the expression of the YPT *aspertase* (*aspA*) gene; the encoded gene product, AspA, subsequently produces ammonia, allowing the ingested organisms to survive the acidic gastrointestinal environment [125]. Other bacterial factors that promote survival under acidic conditions include urease [126], TatC [127], PhoP, OmpR, and PmrA [128, 129]. Acidic pH also induces a downregulation of the transcriptional regulator, Cra (for catabolite repressor/activator), which increases bacterial acid survival [130]. Presumably Cra mediates this action via transcriptional regulation, but its mechanism of action remains unknown.

1.8. T3SS and Yop Effectors. The T3SS, which is encoded on the pYV virulence plasmid and is common to all three pathogenic yersiniae, plays a substantial role in both the establishment and outcome of infection. The T3SS injectisome spans both the inner and outer bacterial membranes, and virulent effector proteins, termed *Yersinia* outer proteins (Yops), are translocated through a host-cell docked *Yersinia* secretion protein F (YscF) needle, directly into the targeted host cells [131]. The YopB and YopD proteins form a pore in the host cell plasma membrane, allowing for the docking of the YscF needle and eventual translocation of the effectors (Figure 3). Proper assembly of a stable injectisome complex also requires the YscE and YscG cytosolic chaperone proteins [132]. There are six effector Yop proteins (YopE, YopH, YopP/J, YopO/YpkA, and YopM) that mediate immune evasion by interfering with host signal transduction pathways, disruption of the host actin cytoskeleton, and by inducing host-cell apoptosis (Figure 3) [133, 134].

Delivery of Yops requires close contact between the bacterial and host cells and is mediated by YadA and invasin through their binding to β1-integrins (Figure 3) [135, 136], which when stimulated cause the activation of Src kinases and RhoA that facilitate Yop translocation via modulation of actin polymerization [137]. In the absence of Yops, activation of β1-integrins would instead lead to actin rearrangements that promote bacterial internalization [138]. Each Yop has a designated chaperone called a Syc protein (for specific Yop chaperone) (e.g., SycE for YopE), required for Yop secretion [133]. The T3SS injectisome is triggered by host-cell contact [139], as well as *in vitro* by temperature (37°C) and low calcium conditions (which serve to emulate intracellular conditions of the host cells) [140–142]. Yop effectors allow evasion of immune responses by blocking host phagocytic function [133, 143, 144], which is vital for bacterial replication and intracellular survival. The *Yersinia* T3SS pore itself was recently suggested to trigger processing of IL-1β and IL-18 in macrophages [75, 145] and subsequent formation of an inflammasome, a cytosolic innate immune complex [146] that triggers inflammation and pyroptosis in response to pore formation [147, 148].

Host cell death is mediated by the YopP/J effector, a serine-threonine acetyltransferase that induces apoptosis of phagocytes by modulating the actions of LPS (Figure 3). Upon binding to the toll-like receptor (TLR)-4, LPS induces the activation of proapoptotic host factors via TRIL (Toll/IL-1 receptor domain-containing adapter inducing IFN-β) [149, 150], while simultaneously downregulating proinflammatory and cell survival genes via inactivation of MAPK and nuclear factor kappa B (NF-κB) transcription factor (Figure 3)

[151–153]. YopP/J specifically inhibits the inflammatory and cell survival actions of LPS [154, 155], thus tipping the scale towards host cell apoptosis [150, 156]. YopP/J-mediated inhibition of host cell proinflammatory responses involves inhibition of IKKβ activation, and thus NF-κB activity (Figure 3) [157], which results in the reduction of TNF-α release by macrophages [158], prevention of IL-8 secretion by epithelial cells [155], and reduction in the presentation of ICAM-1 and E-selectin adhesion factors on the surface of epithelial cells [159]. More recently, it was shown that YopP/J also directly activates caspases (Figure 3) independently of upstream death receptors [160–162].

Once injected into the host-cell cytoplasm, YopE, -H, -P, and -T cooperatively disrupt the cytoskeleton of epithelial cells, macrophages, and dendritic cells thereby decreasing their capacity to engulf the invading bacteria. YopP/J can also facilitate evasion of adaptive immune responses by inhibiting the ability of dendritic cells to present antigens to CD8$^+$ T cells [163], either directly or possibly by decreasing the population of dendritic cells via induction of apoptosis [162, 164, 165]. A similar strategy is employed by YPT using the GTPase activating protein (GAP), YopE, to circumvent phagocytosis by dendritic cells [163, 166]. In addition to the *Yersinia* injectisome and effector proteins, at least three adaptor proteins YopB, YopD, and VirF/LcrV (low calcium response V antigen) are required for T3SS activity [133]. VirF/LcrV (also called V antigen) is a multiple adaptational response (MAR) family member that regulates the T3SS at the level of transcription and, when secreted into the extracellular host environment, contributes to virulence by down-regulating inflammation [167, 168].

YopE, YopT, and YopO/YpkA counteract host-cell phagocytosis by acting on monomeric Rho GTPases responsible for regulation of cytoskeleton dynamics [133]. YopE exhibits GAP activity, thereby inducing GTP hydrolysis and, thus, inactivation of RhoA, Rac1, and Cdc42 (Figure 3) [169–171]. YopT, on the other hand, acts as a cysteine protease that inactivates Rho, Rac, and Cdc42 *via* cleavage [172, 173]. YopO/YpkA is a serine-threonine kinase with sequence and structural similarity to RhoA-binding kinases that undergoes autophosphorylation upon binding to actin [174–176]. YopO can also bind directly to RhoA and Rac-1 with currently unknown consequences [133].

The YopH effector was also recently shown to inhibit host inflammatory responses *via* the downregulation of chemokine monocyte chemoattractant protein 1 (MCP-1) [177]. YopH of YPT inhibits activation of the phosphatidylinositol 3-kinase pathway, resulting in the prevention of antigen-mediated activation of lymphocytes [177, 178]. YopH, a protein tyrosine phosphatase, disrupts T-cell and B-cell activation by interfering with phosphorylation signaling events resulting in decreased expression of the costimulatory molecules B7.2 and CD69, as well as the leukocyte mitogen, IL-2 [178, 179]. Very little is known about YopM, but its deletion results in a dramatic decrease in virulence [180]. YopM appears to be injected into host cells, along with other T3SS effector proteins [181], but there is also evidence that YopM can bind to the extracellular acute phase protein α1-antitrypsin [182]. More recently, YopM was shown to form

a complex with ribosomal S6 kinase (RSK) and protease-activated kinase (PKN) (Figure 3) [183], which results in sustained activation of RSK and possibly contributes to *Yersinia* pathogenicity [184, 185].

1.9. Chromosomal T3SSs. In addition to the pYV-encoded T3SS, there are two additional chromosomally encoded T3SSs in YE: a flagellar T3SS and the Ysa T3SS [186, 187]. The Ysa T3SS is optimally expressed under high salt concentrations, 26°C, and at stationary growth phase [186, 188, 189]. Salt responsiveness is mediated by the sycByspBCDA operon, which is regulated by YsaE and the SycB chaperone [189]. The Ysa T3SS plays a role in virulence [186] and is important for colonization of the small intestine despite its optimal expression at non mammalian temperatures (26°C) [190]. There are 15 known Ysa effector proteins (Ysps), which are thought to function similarly to Yop effectors as modulators of host immune responses [191]. Interestingly, the flagellar T3SS, which functions in the biogenesis of flagella, secretes Fop effectors that also play a role in the pathogenesis of YE [187]. YplA (*Yersinia* phospholipase A), for instance, is a Fop required for colonization of Peyer's Patches and mesenteric lymph nodes that contributes to inflammatory responses within these tissues [192].

1.10. Type VI and IV Secretion System. T3SSs are not the sole secretion systems identified in the yersiniae that promote bacterial virulence. In fact, a type VI secretion system (T6SS) was recently identified in YPT, which harbors four copies, one of which was recently shown to be regulated by temperature, growth phase, and the N-acyl homeserine lactone-AHL-dependent quorum sensing system [193]. YPT also harbors a type IV pilus gene cluster that contributes to pathogenicity [194].

1.11. Host Responses to YE and YPT Infection. *Yersinia* infections are biphasic and are initiated by a "quiet" 36–48 hour period of bacterial replication without a measurable host response. This initial "quiet" phase is followed by an influx of activated phagocytes into infected tissues and lymph nodes, which induces an acute inflammatory response characterized by cytokine production and tissue necrosis [74, 76, 195–199]. The T3SS Yop effectors are likely responsible for the initial inhibition of phagocytic functions, but the mechanisms behind such a sudden, bipolar "off-on" inflammatory response are presently not fully understood. The T3SS is absolutely required for effective colonization of systemic organs, and T3SS inactivation leads to rapid clearance of the bacteria by the host [200–202]. As a result, yersiniae lacking a functional T3SS are avirulent and can function as live attenuated vaccine strains in mice [200, 203, 204].

Recent evidence suggests that macrophages can compensate for YopE/YopH-mediated inhibition of the endosomal MHC class II antigen presentation pathway by an autophagy-dependent mechanism [205]. Thus, autophagy might serve as an alternative counter-pathway by which the host might mount an MHC class II-restricted CD4$^+$ T-cell response

against *Yersinia* T3SS-mediated translocation of Yop virulence effectors [205]. However, whereas Deuretzbacher et al. [206] demonstrated autophagy-mediated degradation of macrophage internalized YE, YPT was shown to usurp the autophagosome pathway for continued replication within macrophages at the intestinal site of infection [207].

Murine studies have demonstrated that CD4+ and CD8+ T cells are required for control of YE infection [196, 208], as are IFN-γ-mediated Th1 immune responses, including macrophage production of TNF, IL-12, and IL-18 [209–212]. Inhibition of T-cell proliferation and dendritic cell functions by Yops are primary mechanisms by which the yersiniae evade both innate and adaptive immune responses [213]. Interestingly, the yersiniae induce both apoptosis of naïve macrophages and inflammatory cell death (pyroptosis) of activated macrophages, which is consistent with its biphasic infection process [73, 75]. Increased inflammation associated with the redirected host cell death could initially benefit the yersiniae but later could contribute to a generalized immune response and eventual clearance of bacteria [73, 75].

1.12. Detection and Prevention of Food-Borne Yersiniosis. YE and YPT clinical infections most often occur following ingestion of the bacteria in contaminated food or water. The two aforementioned yersiniae have been isolated from meat, fresh produce, and milk, but their presence is frequently unapparent due to detection difficulties. Various YE strains are most often distinguished by pulsed-field gel electrophoresis (PFGE), but there is currently no standardized test or database for consistent identification. Moreover, enteropathogenic *Yersinia* species are not included in the protocols that are used by laboratories in PulseNet which, in cooperation with the Association of Public Health Laboratories (APHL), coordinates with public health laboratories to subtype bacterial foodborne pathogens [214]. The heterogeneity of both YE and YPT makes definitive detection difficult, and PFGE produces multiple bands that are not especially distinctive based on serotype [29, 215–217]. Some reports have suggested that current detection methods can produce false-negatives or false-positives based on variability in the presence of *Yersinia* virulence factors, and their variable correlation with pathogenicity [218, 219]. Suggestions for improving detection include the use of more than one restriction nuclease in PFGE analyses [29] and application of a recently developed multilocus variable-number tandem-repeat analysis (MLVA) for YE [220, 221].

Detection is an especially important concern, because both YE and YPT can readily proliferate at refrigeration temperatures (4°C) and even as low as 0°C. Furthermore, the enteropathogenic yersiniae can likewise adapt to and thrive under modified atmospheric conditions that are often used in conjunction with colder temperatures as common methods of food preservation. Survival and cell growth at low temperatures are accomplished via a short-term, cold-shock response, in which a variety of stress response proteins are produced that mediate bacterial adaptation to the sudden drop in temperature (reviewed in [222]). Both YE and YPT are also capable of more long-term cold adaptation, a process

that requires polynucleotide phosphorylase (PNPase), a cold-shock exoribonuclease that enhances both T3SS function as well as promoting growth under cold conditions [223].

Pathogenic YE produce insecticidal toxins, encoded by *tc* (*toxin complex-like*) genes located within a chromosomal pathogenicity island [224, 225]. These insecticidal toxins are expressed at low temperatures [226], but they are nonetheless thought to possess virulence functions in mammalian hosts [224, 225]. It is possible that the presence of these insecticide toxins suggests that the normal life cycle of YE includes an insect stage, as previously proposed [226], and these toxins might facilitate growth of the organisms in refrigerated food products. Tc proteins in YPT, on the other hand, do not possess insecticide activity but rather confer toxicity to mammalian cells [227] and might, therefore, play a role in human disease.

The presence of β-lactamases that confer antibiotic resistance to some pathogenic strains of YE [228, 229] underscores the importance of surveillance for these pathogenic organisms. While these organisms are not monitored nationally, yersiniosis incidence rates and patient demographics in the United States are collected annually by the Foodborne Diseases Active Surveillance Network (FoodNet). FoodNet reported 1,355 and 18 human yersiniosis cases of YE and YPT, respectively, in the U.S. between 1996 and 2007. However, based on FoodNet's assessments [230], cases of yersiniosis, especially those caused by YPT, are likely under-estimated in the U.S. due to lack of testing and difficulty associated with culturing the yersiniae on standard media [231, 232].

2. Conclusions

YE is the major cause of yersiniosis in humans, although prevalence of YPT-associated disease is likely underreported due to lack of surveillance and differences in applied isolation strategies. Extreme heterogeneity among strains of YE and YPT further complicates efforts to link contamination to the source and monitor human disease in a uniform manner comparable to other more thoroughly studied food-borne pathogens (e.g., *Salmonella*). Although a plethora of animal hosts serve as reservoirs for both YE and YPT, human disease-associated yersiniae are most prevalent in swine. In healthy individuals, the resulting illness can manifest as mild, self-limiting diarrhea, but in young children and immunocompromised individuals yersiniosis can represent a significant source of morbidity and mortality. Additionally, chronic diseases, such as reactive arthritis and secondary (or nosocomially derived) complications such as sepsis, can develop in immune compromised persons.

YE and YPT are heterogeneous organisms that differ in genomic content and degree of pathogenicity. Two pathogenic strains (1B/O:8 and 3/O:9) have been sequenced and compared [53, 54] to gain insight into virulence mechanisms required to initiate infection and cause acute symptoms or chronic conditions in patients. YE infection is generally established via consumption of contaminated food or water and involves adherence to and translocation across the intestinal

barrier via M cells [16]. Other virulence factors include the pYV plasmid, which encodes a T3SS essential for YE pathogenicity [79], and the chromosomal HPI locus found in highly pathogenic strains [69]. Pathogenic YPT strains encode a novel superantigenic toxin, YPM that contributes to systemic infections [68] and a PhoP/Q system important for regulation of bacterial survival and growth within macrophages [93, 94]. Type IV pilus genes [194] and a recently discovered T6SS [193] also contribute to yersiniae virulence. While a great deal of molecular work has contributed significantly to a better understanding of YE and YPT pathogenicity, there is much to be gained from future studies, particularly those aimed at dissecting the contributions of various virulence factor combinations to pathogenicity, the resulting type of infection, and ability of the host immune system to clear the bacteria. Very little is known about yersiniae-associated autoimmune disease and other chronic conditions. For instance, YPT is much less studied than YE and thus might be underappreciated as a causative agent of yersiniosis. As such, yersiniosis surveillance efforts concentrate almost exclusively on YE, making attempts to accurately estimate YPT-associated gastroenteritis incidence nearly impossible.

Enteropathogenic YE and YPT cause yersiniosis globally and are of significant concern to the pork industry. The ability of the enteropathogenic yersiniae to replicate and thrive at refrigeration temperatures, coupled with their seemingly ubiquitous nature, suggests that future and more uniform surveillance measures are inevitable and requisite. At present, enteropathogenic yersiniae cases are likely underestimated; however, recent preventative measures in the pork industry and increased attention, both in the research laboratories and clinics, will provide much needed insight and better strategies for managing yersiniosis. Furthermore, more thorough and uniform surveillance measures will allow us to more accurately gauge national and global yersiniosis trends and better predict which agricultural, hygienic, and clinical efforts are effective in reducing the incidence of yersiniosis infection in the general population.

Acknowledgments

References

[1] M. Alexandrino, E. Grohmann, and U. Szewzyk, "Optimization of PCR-based methods for rapid detection of *Campylobacter jejuni*, *Campylobacter coli* and *Yersinia enterocolitica* serovar 0:3 in wastewater samples," *Water Research*, vol. 38, no. 5, pp. 1340–1346, 2004.

[2] N. R. H. El-Maraghi and N. S. Mair, "The histopathology of enteric infection with *Yersinia pseudotuberculosis*," *American Journal of Clinical Pathology*, vol. 71, no. 6, pp. 631–639, 1979.

[3] E. J. Bottone, "*Yersinia enterocolitica*: overview and epidemiologic correlates," *Microbes and Infection*, vol. 1, no. 4, pp. 323–333, 1999.

[4] K. Frölich, J. Wisser, H. Schmüser et al., "Epizootiologic and ecologic investigations of European brown hares (Lepus europaeus) in selected populations from Schleswig-Holstein, Germany," *Journal of Wildlife Diseases*, vol. 39, no. 4, pp. 751–761, 2003.

[5] E. V. Langford, "Pasteurella pseudotuberculosis infections in Western Canada," *Canadian Veterinary Journal*, vol. 13, no. 4, pp. 85–87, 1972.

[6] K. Mühldorfer, G. Wibbelt, J. Haensel, J. Riehm, and S. Speck, "Yersinia species isolated from Bats, Germany," *Emerging Infectious Diseases*, vol. 16, no. 3, pp. 578–580, 2010.

[7] M. Fredriksson-Ahomaa, A. Stolle, A. Siitonen, and H. Korkeala, "Sporadic human *Yersinia enterocolitica* infections caused by bioserotype 4/O:3 originate mainly from pigs," *Journal of Medical Microbiology*, vol. 55, no. 6, pp. 747–749, 2006.

[8] S. Bonardi, A. Paris, L. Bassi et al., "Detection, semiquantitative enumeration, and antimicrobial susceptibility of *Yersinia enterocolitica* in Pork and Chicken Meats in Italy," *Journal of Food Protection*, vol. 73, no. 10, pp. 1785–1792, 2010.

[9] T. F. Jones, S. C. Buckingham, C. A. Bopp, E. Ribot, and W. Schaffner, "From pig to pacifier: chitterling-associated Yersiniosis outbreak among black infants," *Emerging Infectious Diseases*, vol. 9, no. 8, pp. 1007–1009, 2003.

[10] X. Wang, Z. Cui, H. Wang et al., "Pathogenic strains of *Yersinia enterocolitica* isolated from domestic dogs (Canis familiaris) belonging to farmers are of the same subtype as pathogenic *Y. enterocolitica* strains isolated from humans and may be a source of human infection in Jiangsu Province, China," *Journal of Clinical Microbiology*, vol. 48, no. 5, pp. 1604–1610, 2010.

[11] A. Backhans, C. Fellstrom, and S. T. Lambertz, "Occurrence of pathogenic *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* in small wild rodents," *Epidemiology and Infection*, pp. 1–9, 2010.

[12] H. Fukushima, Y. Ito, and K. Saito, "Role of the fly in the transport of *Yersinia enterocolitica*," *Applied and Environmental Microbiology*, vol. 38, no. 5, pp. 1009–1010, 1979.

[13] N. Rahuma, K. S. Ghenghesh, R. Ben Aissa, and A. Elamaari, "Carriage by the housefly (Musca domestica) of multiple-antibiotic-resistant bacteria that are potentially pathogenic to humans, in hospital and other urban environments in Misurata, Libya," *Annals of Tropical Medicine and Parasitology*, vol. 99, no. 8, pp. 795–802, 2005.

[14] M. Lynch, J. Painter, R. Woodruff, and C. Braden, "Surveillance for foodborne-disease outbreaks—United States, 1998–2002," *Morbidity and Mortality Weekly Report*, vol. 55, no. 10, pp. 1–42, 2006.

[15] E. J. Bottone, "*Yersinia enterocolitica*: the charisma continues," *Clinical Microbiology Reviews*, vol. 10, no. 2, pp. 257–276, 1997.

[16] A. Grutzkau, C. Hanski, H. Hahn, and E. O. Riecken, "Involvement of M cells in the bacterial invasion of Peyer's patches: a common mechanism shared by *Yersinia enterocolitica* and other enteroinvasive bacteria," *Gut*, vol. 31, no. 9, pp. 1011–1015, 1990.

[17] J. C. Pepe and V. L. Miller, "The biological role of invasin during a *Yersinia enterocolitica* infection," *Infectious Agents and Disease*, vol. 2, no. 4, pp. 236–241, 1993.

[18] J. C. Pepe and V. L. Miller, "*Yersinia enterocolitica* invasin: a primary role in the initiation of infection," *Proceedings of*

the *National Academy of Sciences of the United States of America*, vol. 90, no. 14, pp. 6473–6477, 1993.

[19] K. Trülzsch, M. F. Oellerich, and J. Heesemann, "Invasion and dissemination of *Yersinia enterocolitica* in the mouse infection model," *Advances in Experimental Medicine and Biology*, vol. 603, pp. 279–285, 2007.

[20] K. Donald, J. Woodson, H. Hudson, and J. O. Menzoian, "Multiple mycotic pseudoaneurysms due to *Yersinia enterocolitica*: report of a case and review of the literature," *Annals of Vascular Surgery*, vol. 10, no. 6, pp. 573–577, 1996.

[21] M. E. Hagensee, "Mycotic aortic aneurysm due to *Yersinia enterocolitica*," *Clinical Infectious Diseases*, vol. 19, no. 4, pp. 801–802, 1994.

[22] B. La Scola, D. Musso, A. Carta, P. Piquet, and J. P. Casalta, "Aortoabdominal aneurysm infected by *Yersinia enterocolitica* serotype O:9," *Journal of Infection*, vol. 35, no. 3, pp. 314–315, 1997.

[23] P. Mercié, P. Morlat, A. N'gako et al., "Aortic aneurysms due to *Yersinia enterocolitica*: three new cases and a review of the literature," *Journal des Maladies Vasculaires*, vol. 21, no. 2, pp. 68–71, 1996.

[24] G. R. Plotkin and J. N. O'Rourke, "Mycotic aneurysm due to *Yersinia enterocolitica*," *American Journal of the Medical Sciences*, vol. 281, no. 1, pp. 35–42, 1981.

[25] M. B. Prentice, N. Fortineau, T. Lambert, A. Voinnesson, and D. Cope, "*Yersinia enterocolitica* and mycotic aneurysm," *Lancet*, vol. 341, no. 8859, pp. 1535–1536, 1993.

[26] S. Tame, D. De Wit, and A. Meek, "*Yersinia enterocolitica* and mycotic aneurysm," *Australian and New Zealand Journal of Surgery*, vol. 68, no. 11, pp. 813–814, 1998.

[27] R. Van Noyen, P. Peeters, F. Van Dessel, and J. Vandepitte, "Mycotic aneurysm of the aorta due to *Yersinia enterocolitica*," *Contributions to Microbiology and Immunology*, vol. 9, pp. 122–126, 1987.

[28] J. Van Steen, J. Vercruysse, G. Wilms, and A. Nevelsteen, "Arteriosclerotic abdominal aortic aneurysm infected with *Yersinia enterocolitica*," *RoFo Fortschritte auf dem Gebiete der Rontgenstrahlen und der Neuen Bildgebenden Verfahren*, vol. 151, no. 5, pp. 625–626, 1989.

[29] M. Fredriksson-Ahomaa, A. Stolle, and H. Korkeala, "Molecular epidemiology of *Yersinia enterocolitica* infections," *FEMS Immunology and Medical Microbiology*, vol. 47, no. 3, pp. 315–329, 2006.

[30] T. L. Cover and R. C. Aber, "*Yersinia enterocolitica*," *New England Journal of Medicine*, vol. 321, no. 1, pp. 16–24, 1989.

[31] H. Fukushima, M. Gomyoda, S. Ishikura et al., "Cat-contaminated environmental substances lead to *Yersinia pseudotuberculosis* infection in children," *Journal of Clinical Microbiology*, vol. 27, no. 12, pp. 2706–2709, 1989.

[32] M. Tsubokura, K. Otsuki, K. Sato et al., "Special features of distribution of *Yersinia pseudotuberculosis* in Japan," *Journal of Clinical Microbiology*, vol. 27, no. 4, pp. 790–791, 1989.

[33] A. Gaulier and F. Poulton, "The place of anatomo-pathological study in the diagnosis of enterocolitis complicated by Yersinia pseudotuberculosis," *Annales de Pathologie*, vol. 3, no. 4, pp. 301–305, 1983.

[34] J. C. Delchier, D. Constantini, and J. C. Soule, "Presence of anti-*Yersinia pseudotuberculosis* agglutinins during a flare-up of ileal Crohn's disease. Apropos of 3 cases," *Gastroenterologie Clinique et Biologique*, vol. 7, no. 6-7, pp. 580–584, 1983.

[35] J. W. Koo, C. R. Cho, S. J. Cha, and C. Y. Chung, "Intussusception associated with *Yersinia pseudotuberculosis* infection," *Acta Paediatrica, International Journal of Paediatrics*, vol. 85, no. 10, pp. 1253–1255, 1996.

[36] J. W. Koo, S. N. Park, S. M. Choi et al., "Acute renal failure associated with *Yersinia pseudotuberculosis* infection in children," *Pediatric Nephrology*, vol. 10, no. 5, pp. 582–586, 1996.

[37] M. V. Tobin, R. E. Meigh, C. L. Smith, and I. T. Gilmore, "*Yersinia pseudotuberculosis* ileitis presenting with severe intestinal haemorrhage," *Journal of the Royal Society of Medicine*, vol. 81, no. 7, pp. 423–424, 1988.

[38] G. Kacerovsky-Bielesz, E. Hentschel, and M. Rotter, "Massive intestinal bleeding caused by *Yersinia pseudotuberculosis*," *Zeitschrift fur Gastroenterologie*, vol. 18, no. 7, pp. 372–375, 1980.

[39] E. Bülbüloğlu, H. Çiralik, B. Kantarçeken, A. Çetinkaya, M. Gül, and F. Ezberci, "*Yersinia pseudotuberculosis* colitis presented with severe gastrointestinal bleeding," *Turkish Journal of Gastroenterology*, vol. 21, no. 2, pp. 179–182, 2010.

[40] R. Tertti, R. Vuento, P. Mikkola, K. Granfors, A. L. Makela, and A. Toivanen, "Clinical manifestations of *Yersinia pseudotuberculosis* infection in children," *European Journal of Clinical Microbiology and Infectious Diseases*, vol. 8, no. 7, pp. 587–591, 1989.

[41] H. Grant, H. Rode, and S. Cywes, "*Yersinia pseudotuberculosis* affecting the appendix," *Journal of Pediatric Surgery*, vol. 29, no. 12, p. 1621, 1994.

[42] A. I. Parfenov and M. D. Chizhikova, "Chronic and lingering Yersinia ileitis," *Terapevticheskii Arkhiv*, vol. 74, no. 12, pp. 77–80, 2002.

[43] L. K. Logsdon and J. Mecsas, "Requirement of the *Yersinia pseudotuberculosis* effectors YopH and YopE in colonization and persistence in intestinal and lymph tissues," *Infection and Immunity*, vol. 71, no. 8, pp. 4595–4607, 2003.

[44] N. S. Mair, E. Fox, and E. Thal, "Biochemical, pathogenicity and toxicity studies of type III strains of *Yersinia pseudotuberculosis* isolated from the cecal contents of pigs," *Contributions to Microbiology and Immunology*, vol. 5, pp. 359–365, 1979.

[45] A. G. Deacon, A. Hay, and J. Duncan, "Septicemia due to *Yersinia pseudotuberculosis*—a case report," *Clinical Microbiology and Infection*, vol. 9, no. 11, pp. 1118–1119, 2003.

[46] M. Nakamura, T. Shikano, and N. Ueno, "A case of *Yersinia pseudotuberculosis* septicemia accompanied by a large abdominal tumor," *Clinical Pediatrics*, vol. 23, no. 2, pp. 121–123, 1984.

[47] M. Macari, J. Hines, E. Balthazar, and A. Megibow, "Mesenteric adenitis: CT diagnosis of primary versus secondary causes, incidence, and clinical significance in pediatric and adult patients," *American Journal of Roentgenology*, vol. 178, no. 4, pp. 853–858, 2002.

[48] N. Konishi, K. Baba, J. Abe et al., "A case of Kawasaki disease with coronary artery aneurysms documenting *Yersinia pseudotuberculosis* infection," *Acta Paediatrica, International Journal of Paediatrics*, vol. 86, no. 6, pp. 661–664, 1997.

[49] B. M. Rosner, K. Stark, and D. Werber, "Epidemiology of reported *Yersinia enterocolitica* infections in Germany, 2001–2008," *BMC Public Health*, vol. 10, article 337, 2010.

[50] R. M. Robins-Browne, M. D. Miliotis, S. Cianciosi, V. L. Miller, S. Falkow, and J. G. Morris Jr., "Evaluation of DNA colony hybridization and other techniques for detection of virulence in Yersinia species," *Journal of Clinical Microbiology*, vol. 27, no. 4, pp. 644–650, 1989.

[51] X. Wang, Z. Cui, D. Jin et al., "Distribution of pathogenic *Yersinia enterocolitica* in China," *European Journal of Clinical Microbiology and Infectious Diseases*, vol. 28, no. 10, pp. 1237–1244, 2009.

[52] A. McNally, T. Cheasty, C. Fearnley et al., "Comparison of the biotypes of *Yersinia enterocolitica* isolated from pigs, cattle

and sheep at slaughter and from humans with yersiniosis in Great Britain during 1999-2000," *Letters in Applied Microbiology*, vol. 39, no. 1, pp. 103–108, 2004.

[53] N. R. Thomson, S. Howard, B. W. Wren et al., "The complete genome sequence and comparative genome analysis of the high pathogenicity *Yersinia enterocolitica* strain 8081.," *PLoS genetics*, vol. 2, no. 12, article e206, 2006.

[54] X. Wang, Y. Li, H. Jing et al., "Complete genome sequence of a *Yersinia enterocolitica* "old world" (3/o:9) strain and comparison with the "new world" (1B/O:8) strain," *Journal of Clinical Microbiology*, vol. 49, no. 4, pp. 1251–1259, 2011.

[55] C. Pelludat, A. Rakin, C. A. Jacobi, S. Schubert, and J. Heesemann, "The yersiniabactin biosynthetic gene cluster of *Yersinia enterocolitica*: organization and siderophore-dependent regulation," *Journal of Bacteriology*, vol. 180, no. 3, pp. 538–546, 1998.

[56] A. Iwobi, J. Heesemann, E. Garcia, E. Igwe, C. Noelting, and A. Rakin, "Novel virulence-associated type II secretion system unique to high-pathogenicity *Yersinia enterocolitica*," *Infection and Immunity*, vol. 71, no. 4, pp. 1872–1879, 2003.

[57] L. A. Lee, J. Taylor, G. P. Carter, B. Quinn, J. J. Farmer III, and R. V. Tauxe, "*Yersinia enterocolitica* O:3: an emerging cause of pediatric gastroenteritis in the United States," *Journal of Infectious Diseases*, vol. 163, no. 3, pp. 660–663, 1991.

[58] M. Tsubokura and S. Aleksić, "A simplified antigenic scheme for serotyping of *Yersinia pseudotuberculosis*: phenotypic characterization of reference strains and preparation of O and H factor sera," *Contributions to Microbiology and Immunology*, vol. 13, pp. 99–105, 1995.

[59] H. Fukushima, M. Gomyoda, N. Hashimoto et al., "Putative origin of *Yersinia pseudotuberculosis* in Western and Eastern countries. A comparison of restriction endonuclease analysis of virulence plasmids," *Zentralblatt fur Bakteriologie*, vol. 288, no. 1, pp. 93–102, 1998.

[60] H. Fukushima, M. Gomyoda, and S. Kaneko, "Mice and moles inhabiting mountainous areas of Shimane Peninsula as sources of infection with *Yersinia pseudotuberculosis*," *Journal of Clinical Microbiology*, vol. 28, no. 11, pp. 2448–2455, 1990.

[61] H. Fukushima, M. Tsubokura, and K. Otsuki, "Epidemiological study of *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* infections in Shimane Prefecture, Japan," *Zentralblatt fur Bakteriologie Mikrobiologie und Hygiene*, vol. 180, no. 5-6, pp. 515–527, 1985.

[62] T. M. Bogdanovich, E. Carniel, H. Fukushima, and M. Skurnik, "Genetic (sero) typing of *Yersinia pseudotuberculosis*," *Advances in Experimental Medicine and Biology*, vol. 529, pp. 337–340, 2003.

[63] H. Fukushima, Y. Matsuda, R. Seki et al., "Geographical heterogeneity between Far Eastern and western countries in prevalence of the virulence plasmid, the superantigen *Yersinia pseudotuberculosis*-derived mitogen, and the high-pathogenicity island among *Yersinia pseudotuberculosis* strains," *Journal of Clinical Microbiology*, vol. 39, no. 10, pp. 3541–3547, 2001.

[64] C. Buchrieser, R. Brosch, S. Bach, A. Guiyoule, and E. Carniel, "The high-pathogenicity island of *Yersinia pseudotuberculosis* can be inserted into any of the three chromosomal asn tRNA genes," *Molecular Microbiology*, vol. 30, no. 5, pp. 965–978, 1998.

[65] A. M. P. De Almeida, A. Guiyoule, I. Guilvout, I. Iteman, G. Baranton, and E. Carniel, "Chromosomal irp2 gene in Yersinia: distribution, expression, deletion and impact on virulence," *Microbial Pathogenesis*, vol. 14, no. 1, pp. 9–21, 1993.

[66] A. Rakin, P. Urbitsch, and J. Heesemann, "Evidence for two evolutionary lineages of highly pathogenic Yersinia species," *Journal of Bacteriology*, vol. 177, no. 9, pp. 2292–2298, 1995.

[67] G. R. Cornelis, T. Biot, C. Lambert de Rouvroit et al., "The Yersinia yop regulon," *Molecular Microbiology*, vol. 3, no. 10, pp. 1455–1459, 1989.

[68] C. Carnoy, C. Mullet, H. Müller-Alouf, E. Leteurtre, and M. Simonet, "Superantigen YPMa exacerbates the virulence of *Yersinia pseudotuberculosis* in mice," *Infection and Immunity*, vol. 68, no. 5, pp. 2553–2559, 2000.

[69] E. Carniel, "The Yersinia high-pathogenicity island," *International Microbiology*, vol. 2, no. 3, pp. 161–167, 1999.

[70] J. Abe and T. Takeda, "Characterization of a superantigen produced by *Yersinia pseudotuberculosis*," *Preparative Biochemistry and Biotechnology*, vol. 27, no. 2-3, pp. 173–208, 1997.

[71] H. Ueshiba, H. Kato, T. Miyoshi-Akiyama et al., "Analysis of the superantigen-producing ability of *Yersinia pseudotuberculosis* strains of various serotypes isolated from patients with systemic or gastroenteric infections, wildlife animals and natural environments," *Zentralblatt fur Bakteriologie*, vol. 288, no. 2, pp. 277–291, 1998.

[72] K. I. Yoshino, T. Ramamurthy, G. B. Nair et al., "Geographical heterogeneity between Far East and Europe in prevalence of ypm gene encoding the novel superantigen among *Yersinia pseudotuberculosis* strains," *Journal of Clinical Microbiology*, vol. 33, no. 12, pp. 3356–3358, 1995.

[73] T. Bergsbaken and B. T. Cookson, "Innate immune response during Yersinia infection: critical modulation of cell death mechanisms through phagocyte activation," *Journal of Leukocyte Biology*, vol. 86, no. 5, pp. 1153–1158, 2009.

[74] F. Sebbane, D. Gardner, D. Long, B. B. Gowen, and B. J. Hinnebusch, "Kinetics of disease progression and host response in a rat model of bubonic plague," *American Journal of Pathology*, vol. 166, no. 5, pp. 1427–1439, 2005.

[75] T. Bergsbaken and B. T. Cookson, "Macrophage activation redirects yersinia-infected host cell death from apoptosis to caspase-1-dependent pyroptosis," *PLoS Pathogens*, vol. 3, no. 11, article e161, 2007.

[76] F. Guinet, P. Avé, L. Jones, M. Huerre, and E. Carniel, "Defective innate cell response and lymph node infiltration specify Yersinia pestis infection," *PLoS ONE*, vol. 3, no. 2, Article ID e1688, 2008.

[77] R. R. Brubaker, "Factors promoting acute and chronic diseases caused by yersiniae," *Clinical Microbiology Reviews*, vol. 4, no. 3, pp. 309–324, 1991.

[78] P. Gemski, J. R. Lazere, T. Casey, and J. A. Wohlhieter, "Presence of a virulence-associated plasmid in *Yersinia pseudotuberculosis*," *Infection and Immunity*, vol. 28, no. 3, pp. 1044–1047, 1980.

[79] D. A. Portnoy and S. Falkow, "Virulence-associated plasmids from *Yersinia enterocolitica* and Yersinia pestis," *Journal of Bacteriology*, vol. 148, no. 3, pp. 877–883, 1981.

[80] A. M. Gehring, E. DeMoll, J. D. Fetherston et al., "Iron acquisition in plague: modular logic in enzymatic biogenesis of yersiniabactin by Yersinia pestis," *Chemistry and Biology*, vol. 5, no. 10, pp. 573–586, 1998.

[81] A. Rakin, C. Noelting, S. Schubert, and J. Heesemann, "Common and specific characteristics of the high-pathogenicity island of *Yersinia enterocolitica*," *Infection and Immunity*, vol. 67, no. 10, pp. 5265–5274, 1999.

[82] J. D. Fetherston, S. W. Bearden, and R. D. Perry, "YbtA, an AraC-type regulator of the Yersinia pestis pesticin/yersiniabactin receptor," *Molecular Microbiology*, vol. 22, no. 2, pp. 315–325, 1996.

[83] J. Heesemann, K. Hantke, T. Vocke a et al., "Virulence of *Yersinia enterocolitica* is closely associated with siderophore production, expression of an iron-repressible outer membrane polypeptide of 65,000 Da and pesticin sensitivity," *Molecular Microbiology*, vol. 8, no. 2, pp. 397–408, 1993.

[84] E. Carniel, "The Yersinia high-pathogenicity island: an iron-uptake island," *Microbes and Infection*, vol. 3, no. 7, pp. 561–569, 2001.

[85] E. Carniel, I. Guilvout, and M. Prentice, "Characterization of a large chromosomal "high-pathogenicity island" in biotype 1B *Yersinia enterocolitica*," *Journal of Bacteriology*, vol. 178, no. 23, pp. 6743–6751, 1996.

[86] J. Abe, T. Takeda, Y. Watanabe et al., "Evidence for super-antigen production by *Yersinia pseudotuberculosis*," *Journal of Immunology*, vol. 151, no. 8, pp. 4183–4188, 1993.

[87] T. Uchiyama, T. Miyoshi-Akiyama, H. Kato, W. Fujimaki, K. Imanishi, and X. J. Yan, "Superantigenic properties of a novel mitogenic substance produced by *Yersinia pseudotuberculosis* isolated from patients manifesting acute and systemic symptoms," *Journal of Immunology*, vol. 151, no. 8, pp. 4407–4413, 1993.

[88] T. Ramamurthy, K. I. Yoshino, J. Abe, N. Ikeda, and T. Takeda, "Purification, characterization and cloning of a novel variant of the superantigen Yersinia pseudotuberculosis-derived mitogen," *FEBS Letters*, vol. 413, no. 1, pp. 174–176, 1997.

[89] C. Carnoy, S. Floquet, M. Marceau et al., "The superantigen gene ypm is located in an unstable chromosomal locus of *Yersinia pseudotuberculosis*," *Journal of Bacteriology*, vol. 184, no. 16, pp. 4489–4499, 2002.

[90] C. A. Schiano, L. E. Bellows, and W. W. Lathem, "The small RNA chaperone Hfq is required for the virulence of *Yersinia pseudotuberculosis*," *Infection and Immunity*, vol. 78, no. 5, pp. 2034–2044, 2010.

[91] H. Nakao, H. Watanabe, S. I. Nakayama, and T. Takeda, "Yst gene expression in *Yersinia enterocolitica* is positively regulated by a chromosomal region that is highly homologous to Escherichia coli host factor 1 gene (hfq)," *Molecular Microbiology*, vol. 18, no. 5, pp. 859–865, 1995.

[92] E. A. Groisman, "The pleiotropic two-component regulatory system PhoP-PhoQ," *Journal of Bacteriology*, vol. 183, no. 6, pp. 1835–1842, 2001.

[93] J. P. Grabenstein, M. Marceau, C. Pujol, M. Simonet, and J. B. Bliska, "The response regulator PhoP of *Yersinia pseudotuberculosis* is important for replication in macrophages and for virulence," *Infection and Immunity*, vol. 72, no. 9, pp. 4973–4984, 2004.

[94] P. C. F. Oyston, N. Dorrell, K. Williams et al., "The response regulator PhoP is important for survival under conditions of macrophage-induced stress and virulence in Yersinia pestis," *Infection and Immunity*, vol. 68, no. 6, pp. 3419–3425, 2000.

[95] R. Rebeil, R. K. Ernst, B. B. Gowen, S. I. Miller, and B. J. Hinnebusch, "Variation in lipid A structure in the pathogenic yersiniae," *Molecular Microbiology*, vol. 52, no. 5, pp. 1363–1373, 2004.

[96] O. L. Champion, A. V. Karlyshev, I. A. Cooper et al., "*Yersinia pseudotuberculosis* mntH functions in intracellular manganese accumulation that is essential for virulence and survival in cells expressing functional Nramp1," *Microbiology*, vol. 157, part 4, pp. 1115–1122, 2011.

[97] H. Matsumoto and G. M. Young, "Translocated effectors of Yersinia," *Current Opinion in Microbiology*, vol. 12, no. 1, pp. 94–100, 2009.

[98] D. W. Ellison, M. B. Lawrenz, and V. L. Miller, "Invasin and beyond: regulation of Yersinia virulence by RovA," *Trends in Microbiology*, vol. 12, no. 6, pp. 296–300, 2004.

[99] D. W. Ellison, B. Young, K. Nelson, and V. L. Miller, "YmoA negatively regulates expression of invasin from *Yersinia enterocolitica*," *Journal of Bacteriology*, vol. 185, no. 24, pp. 7153–7159, 2003.

[100] D. W. Ellison and V. L. Miller, "H-NS represses inv transcription in *Yersinia enterocolitica* through competition with RovA and interaction with YmoA," *Journal of Bacteriology*, vol. 188, no. 14, pp. 5101–5112, 2006.

[101] D. W. Ellison and V. L. Miller, "Regulation of virulence by members of the MarR/SlyA family," *Current Opinion in Microbiology*, vol. 9, no. 2, pp. 153–159, 2006.

[102] G. Nagel, A. Lahrz, and P. Dersch, "Environmental control of invasin expression in *Yersinia pseudotuberculosis* is mediated by regulation of RovA, a transcriptional activator of the SlyA/Hor family," *Molecular Microbiology*, vol. 41, no. 6, pp. 1249–1269, 2001.

[103] P. A. Revell and V. L. Miller, "A chromosomally encoded regulator is required for expression of the *Yersinia enterocolitica* inv gene and for virulence," *Molecular Microbiology*, vol. 35, no. 3, pp. 677–685, 2000.

[104] G. Balligand, Y. Laroche, and G. Cornelis, "Genetic analysis of virulence plasmid from a serogroup 9 *Yersinia enterocolitica* strain: role of outer membrane protein P1 in resistance to human serum and autoagglutination," *Infection and Immunity*, vol. 48, no. 3, pp. 782–786, 1985.

[105] T. Heise and P. Dersch, "Identification of a domain in Yersinia virulence factor YadA that is crucial for extracellular matrix-specific cell adhesion and uptake," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, no. 9, pp. 3375–3380, 2006.

[106] R. J. Martinez, "Thermoregulation-dependent expression of *Yersinia enterocolitica* protein 1 imparts serum resistance to Escherichia coli K-12," *Journal of Bacteriology*, vol. 171, no. 7, pp. 3732–3739, 1989.

[107] G. R. Cornelis and H. Wolf-Watz, "The Yersinia Yop virulon: a bacterial system for subverting eukaryotic cells," *Molecular Microbiology*, vol. 23, no. 5, pp. 861–867, 1997.

[108] M. Skurnik and P. Toivanen, "LcrF is the temperature-regulated activator of the yadA gene of *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*," *Journal of Bacteriology*, vol. 174, no. 6, pp. 2047–2051, 1992.

[109] J. C. Pepe, M. R. Wachtel, E. Wagar, and V. L. Miller, "Pathogenesis of defined invasion mutants of *Yersinia enterocolitica* in a BALB/c mouse model of infection," *Infection and Immunity*, vol. 63, no. 12, pp. 4837–4848, 1995.

[110] I. Bolin and H. Wolf Watz, "Molecular cloning of the temperature-inducible outer membrane protein 1 of *Yersinia pseudotuberculosis*," *Infection and Immunity*, vol. 43, no. 1, pp. 72–78, 1984.

[111] Y. W. Han and V. L. Miller, "Reevaluation of the virulence phenotype of the inv yada double mutants of *Yersinia pseudotuberculosis*," *Infection and Immunity*, vol. 65, no. 1, pp. 327–330, 1997.

[112] R. Rosqvist, M. Skurnik, and H. Wolf-Watz, "Increased virulence of *Yersinia pseudotuberculosis* by two independent mutations," *Nature*, vol. 334, no. 6182, pp. 522–525, 1988.

[113] J. Eitel, T. Heise, U. Thiesen, and P. Dersch, "Cell invasion and IL-8 production pathways initiated by YadA of *Yersinia pseudotuberculosis* require common signalling molecules (FAK, c-Src, Ras) and distinct cell factors," *Cellular Microbiology*, vol. 7, no. 1, pp. 63–77, 2005.

[114] Y. Schmid, G. A. Grassl, O. T. Bühler, M. Skurnik, I. B. Autenrieth, and E. Bohn, "*Yersinia enterocolitica* adhesin A induces production of interleukin-8 in epithelial cells," *Infection and Immunity*, vol. 72, no. 12, pp. 6780–6789, 2004.

[115] O. Laitenen, J. Tuuhea, and P. Ahvonen, "Polyarthritis associated with *Yersinia enterocolitica* infection. Clinical features and laboratory findings in nine cases with severe joint symptoms," *Annals of the Rheumatic Diseases*, vol. 31, no. 1, pp. 34–39, 1972.

[116] O. Laitinen, M. Leirisalo, and G. Skylv, "Relation between HLA-B27 and clinical features in patients with yersinia arthritis," *Arthritis and Rheumatism*, vol. 20, no. 5, pp. 1121–1124, 1977.

[117] R. Lahesmaa, E. Eerola, and A. Toivanen, "Does reduced erythrocyte C3b receptor (CR1) activity contribute to the pathogenesis of yersinia triggered reactive arthritis?" *Annals of the Rheumatic Diseases*, vol. 51, no. 1, pp. 97–100, 1992.

[118] R. Lahesmaa, H. Yssel, S. Batsford et al., "*Yersinia enterocolitica* activates a T helper type 1-like T cell subset in reactive arthritis," *Journal of Immunology*, vol. 148, no. 10, pp. 3079–3085, 1992.

[119] M. Skurnik, "Role of YadA in Yersinia-enterocolitica-induced reactive arthritis: a hypothesis," *Trends in Microbiology*, vol. 3, no. 8, pp. 318–319, 1995.

[120] M. Biedzka-Sarek, H. Jarva, H. Hyytiäinen, S. Meri, and M. Skurnik, "Characterization of complement factor H binding to *Yersinia enterocolitica* serotype O:3," *Infection and Immunity*, vol. 76, no. 9, pp. 4100–4109, 2008.

[121] M. Biedzka-Sarek, S. Salmenlinna, M. Gruber, A. N. Lupas, S. Meri, and M. Skurnik, "Functional mapping of YadA- and Ail-mediated binding of human factor H to *Yersinia enterocolitica* serotype O:3," *Infection and Immunity*, vol. 76, no. 11, pp. 5016–5027, 2008.

[122] M. Biedzka-Sarek, R. Venho, and M. Skurnik, "Role of YadA, Ail, and lipopolysaccharide in serum resistance of *Yersinia enterocolitica* serotype O:3," *Infection and Immunity*, vol. 73, no. 4, pp. 2232–2244, 2005.

[123] V. Kirjavainen, H. Jarva, M. Biedzka-Sarek, A. M. Blom, M. Skurnik, and S. Meri, "*Yersinia enterocolitica* serum resistance proteins YadA and ail bind the complement regulator C4b-binding protein," *PLoS Pathogens*, vol. 4, no. 8, Article ID e1000140, 2008.

[124] F. Pouillot, C. Fayolle, and E. Carniel, "A putative DNA adenine methyltransferase is involved in *Yersinia pseudotuberculosis* pathogenicity," *Microbiology*, vol. 153, no. 8, pp. 2426–2434, 2007.

[125] Y. Hu, P. Lu, Y. Zhang, L. Li, and S. Chen, "Characterization of an aspartate-dependent acid survival system in *Yersinia pseudotuberculosis*," *FEBS Letters*, vol. 584, no. 11, pp. 2311–2314, 2010.

[126] B. Riot, P. Berche, and M. Simonet, "Urease is not involved in the virulence of *Yersinia pseudotuberculosis* in mice," *Infection and Immunity*, vol. 65, no. 5, pp. 1985–1990, 1997.

[127] M. Lavander, S. K. Ericsson, J. E. Bröms, and A. Forsberg, "The twin arginine translocation system is essential for virulence of *Yersinia pseudotuberculosis*," *Infection and Immunity*, vol. 74, no. 3, pp. 1768–1776, 2006.

[128] C. Flamez, I. Ricard, S. Arafah, M. Simonet, and M. Marceau, "Phenotypic analysis of *Yersinia pseudotuberculosis* 32777 response regulator mutants: new insights into two-component system regulon plasticity in bacteria," *International Journal of Medical Microbiology*, vol. 298, no. 3-4, pp. 193–207, 2008.

[129] Y. Hu, P. Lu, Y. Wang, L. Ding, S. Atkinson, and S. Chen, "OmpR positively regulates urease expression to enhance acid survival of *Yersinia pseudotuberculosis*," *Microbiology*, vol. 155, no. 8, pp. 2522–2531, 2009.

[130] Y. Hu, P. Lu, Y. Zhang et al., "Cra negatively regulates acid survival in *Yersinia pseudotuberculosis*," *FEMS Microbiology Letters*, vol. 317, no. 2, pp. 190–195, 2011.

[131] G. R. Cornelis, "The type III secretion injectisome," *Nature Reviews Microbiology*, vol. 4, no. 11, pp. 811–825, 2006.

[132] M. Quinaud, J. Chabert, E. Faudry et al., "The PscE-PscF-PscG complex controls type III secretion needle biogenesis in Pseudomonas aeruginosa," *Journal of Biological Chemistry*, vol. 280, no. 43, pp. 36293–36300, 2005.

[133] G. R. Cornelis, "Yersinia type III secretion: send in the effectors," *Journal of Cell Biology*, vol. 158, no. 3, pp. 401–408, 2002.

[134] J. E. Trosky, A. D. B. Liverman, and K. Orth, "Yersinia outer proteins: Yops," *Cellular Microbiology*, vol. 10, no. 3, pp. 557–565, 2008.

[135] J. Eitel and P. Dersch, "The YadA protein of *Yersinia pseudotuberculosis* mediates high-efficiency uptake into human cells under environmental conditions in which invasin is repressed," *Infection and Immunity*, vol. 70, no. 9, pp. 4880–4891, 2002.

[136] R. R. Isberg and J. M. Leong, "Multiple $\beta 1$ chain integrins are receptors for invasin, a protein that promotes bacterial penetration into mammalian cells," *Cell*, vol. 60, no. 5, pp. 861–871, 1990.

[137] E. Mejía, J. B. Bliska, and G. I. Viboud, "Yersinia controls type III effector delivery into host cells by modulating Rho activity," *PLoS Pathogens*, vol. 4, no. 1, article 3, 2008.

[138] S. Mohammadi and R. R. Isberg, "*Yersinia pseudotuberculosis* virulence determinants invasin, YopE, and YopT modulate RhoG activity and localization," *Infection and Immunity*, vol. 77, no. 11, pp. 4771–4782, 2009.

[139] J. Pettersson, R. Nordfelth, E. Dubinina et al., "Modulation of virulence factor expression by pathogen target cell contact," *Science*, vol. 273, no. 5279, pp. 1231–1233, 1996.

[140] V. L. Motin, A. M. Georgescu, J. P. Fitch et al., "Temporal global changes in gene expression during temperature transition in Yersinia pestis," *Journal of Bacteriology*, vol. 186, no. 18, pp. 6298–6305, 2004.

[141] S. C. Straley and R. D. Perry, "Environmental modulation of gene expression and pathogenesis in Yersinia," *Trends in Microbiology*, vol. 3, no. 8, pp. 310–317, 1995.

[142] S. C. Straley, G. V. Plano, E. Skrzypek, P. L. Haddix, and K. A. Fields, "Regulation by Ca2+ in the Yersinia low-Ca2+ response," *Molecular Microbiology*, vol. 8, no. 6, pp. 1005–1010, 1993.

[143] G. R. Cornelis, A. Boland, A. P. Boyd et al., "The virulence plasmid of Yersinia, an antihost genome," *Microbiology and Molecular Biology Reviews*, vol. 62, no. 4, pp. 1315–1352, 1998.

[144] G. I. Viboud and J. B. Bliska, "Yersinia outer proteins: role in modulation of host cell signaling responses and pathogenesis," *Annual Review of Microbiology*, vol. 59, pp. 69–89, 2005.

[145] H. Shin and G. R. Cornelis, "Type III secretion translocation pores of *Yersinia enterocolitica* trigger maturation and release of pro-inflammatory IL-1β," *Cellular Microbiology*, vol. 9, no. 12, pp. 2893–2902, 2007.

[146] V. Petrilli, S. Papin, and J. Tschopp, "The inflammasome," *Current Biology*, vol. 15, no. 15, p. R581, 2005.

[147] F. L. van de Veerdonk, M. G. Netea, C. A. Dinarello, and L. A. Joosten, "Inflammasome activation and IL-1beta and IL-18 processing during infection," *Trends in Immunology*, vol. 32, no. 3, pp. 110–116, 2011.

[148] E. A. Miao, I. A. Leaf, P. M. Treuting et al., "Caspase-1-induced pyroptosis is an innate immune effector mechanism against intracellular bacteria," *Nature Immunology*, vol. 11, no. 12, pp. 1136–1142, 2010.

[149] K. Hoebe, X. Du, P. Georgel et al., "Identification of Lps2 as a key transducer of MyD88-independent TIR signalling," *Nature*, vol. 424, no. 6950, pp. 743–748, 2003.

[150] K. Ruckdeschel, G. Pfaffinger, R. Haase et al., "Signaling of apoptosis through TLRs critically involves toll/IL-1 receptor domain-containing adapter inducing IFN-β, but not MyD88, in bacteria-infected murine macrophages," *Journal of Immunology*, vol. 173, no. 5, pp. 3320–3328, 2004.

[151] M. Karin and A. Lin, "NF-κB at the crossroads of life and death," *Nature Immunology*, vol. 3, no. 3, pp. 221–227, 2002.

[152] J. M. Park, F. R. Greten, A. Wong et al., "Signaling pathways and genes that inhibit pathogen-induced macrophage apoptosis - CREB and NF-κB as key regulators," *Immunity*, vol. 23, no. 3, pp. 319–329, 2005.

[153] Y. Zhang, A. T. Ting, K. B. Marcu, and J. B. Bliska, "Inhibition of MAPK and NF-κB pathways is necessary for rapid apoptosis in macrophages infected with Yersinia," *Journal of Immunology*, vol. 174, no. 12, pp. 7939–7949, 2005.

[154] L. E. Palmer, S. Hobble, J. E. Galán, and J. B. Bliska, "YopJ of *Yersinia pseudotuberculosis* is required for the inhibition of macrophage TNF-α production and downregulation of the MAP kinases p38 and JNK," *Molecular Microbiology*, vol. 27, no. 5, pp. 953–965, 1998.

[155] K. Schesser, A. K. Spiik, J. M. Dukuzumuremyi, M. F. Neurath, S. Pettersson, and H. Wolf-Watz, "The yopJ locus is required for Yersinia-mediated inhibition of NF-κB activation and cytokine expression: YopJ contains a eukaryotic SH2-like domain that is essential for its repressive activity," *Molecular Microbiology*, vol. 28, no. 6, pp. 1067–1079, 1998.

[156] G. Denecker, W. Declercq, C. A. W. Geuijen et al., "*Yersinia enterocolitica* YopP-induced apoptosis of macrophages involves the apoptotic signaling cascade upstream of bid," *Journal of Biological Chemistry*, vol. 276, no. 23, pp. 19706–19714, 2001.

[157] K. Orth, L. E. Palmer, Z. Q. Bao et al., "Inhibition of the mitogen-activated protein kinase kinase superfamily by a Yersinia effector," *Science*, vol. 285, no. 5435, pp. 1920–1923, 1999.

[158] A. Boland and G. R. Cornelis, "Role of YopP in suppression of tumor necrosis factor alpha release by macrophages during Yersinia infection," *Infection and Immunity*, vol. 66, no. 5, pp. 1878–1884, 1998.

[159] G. Denecker, S. Tötemeyer, L. J. Mota et al., "Effect of low- and high-virulence *Yersinia enterocolitica* strains on the inflammatory response of human umbilical vein endothelial cells," *Infection and Immunity*, vol. 70, no. 7, pp. 3510–3520, 2002.

[160] S. Gröbner, S. E. Autenrieth, I. Soldanova et al., "Yersinia YopP-induced apoptotic cell death in murine dendritic cells is partially independent from action of caspases and exhibits necrosis-like features," *Apoptosis*, vol. 11, no. 11, pp. 1959–1968, 2006.

[161] S. Gröbner, I. Adkins, S. Schulz et al., "Catalytically active Yersinia outer protein P induces cleavage of RIP and caspase-8 at the level of the DISC independently of death receptors

in dendritic cells," *Apoptosis*, vol. 12, no. 10, pp. 1813–1825, 2007.

[162] S. E. Erfurth, S. Gröbner, U. Kramer et al., "*Yersinia enterocolitica* induces apoptosis and inhibits surface molecule expression and cytokine production in murine dendritic cells," *Infection and Immunity*, vol. 72, no. 12, pp. 7045–7054, 2004.

[163] S. Bedoui, A. Kupz, O. L. Wijburg, A. K. Walduck, M. Rescigno, and R. A. Strugnell, "Different bacterial pathogens, different strategies, yet the aim is the same: evasion of intestinal dendritic cell recognition," *Journal of Immunology*, vol. 184, no. 5, pp. 2237–2242, 2010.

[164] K. Trülzsch, G. Geginat, T. Sporleder et al., "Yersinia outer protein P inhibits CD8 T cell priming in the mouse infection model," *Journal of Immunology*, vol. 174, no. 7, pp. 4244–4251, 2005.

[165] S. E. Autenrieth, I. Soldanova, R. Rösemann et al., "*Yersinia enterocolitica* YopP inhibits MAP kinase-mediated antigen uptake in dendritic cells," *Cellular Microbiology*, vol. 9, no. 2, pp. 425–437, 2007.

[166] A. Fahlgren, L. Westermark, K. Akopyan, and M. Fällman, "Cell type-specific effects of *Yersinia pseudotuberculosis* virulence effectors," *Cellular Microbiology*, vol. 11, no. 12, pp. 1750–1767, 2009.

[167] L. K. Garrity-Ryan, O. K. Kim, J. M. Balada-Llasat et al., "Small molecule inhibitors of LcrF, a *Yersinia pseudotuberculosis* transcription factor, attenuate virulence and limit infection in a murine pneumonia model," *Infection and Immunity*, vol. 78, no. 11, pp. 4683–4690, 2010.

[168] R. R. Brubaker, "Interleukin-10 and inhibition of innate immunity to Yersiniae: roles of Yops and LcrV (V antigen)," *Infection and Immunity*, vol. 71, no. 7, pp. 3673–3681, 2003.

[169] R. Rosqvist, A. Forsberg, M. Rimpilainen, T. Bergman, and H. Wolf-Watz, "The cytotoxic protein YopE of Yersinia obstructs the primary host defence," *Molecular Microbiology*, vol. 4, no. 4, pp. 657–667, 1990.

[170] D. S. Black and J. B. Bliska, "The RhoGAP activity of the *Yersinia pseudotuberculosis* cytotoxin YopE is required for antiphagocytic function and virulence," *Molecular Microbiology*, vol. 37, no. 3, pp. 515–527, 2000.

[171] U. Von Pawel-Rammingen, M. V. Telepnev, G. Schmidt, K. Aktories, H. Wolf-Watz, and R. Rosqvist, "GAP activity of the Yersinia YopE cytotoxin specifically targets the Rho pathway: a mechanism for disruption of actin microfilament structure," *Molecular Microbiology*, vol. 36, no. 3, pp. 737–748, 2000.

[172] M. Iriarte and G. R. Cornelis, "YopT, a new Yersinia Yop effector protein, affects the cytoskeleton of host cells," *Molecular Microbiology*, vol. 29, no. 3, pp. 915–929, 1998.

[173] F. Shao, P. M. Merritt, Z. Bao, R. W. Innes, and J. E. Dixon, "A Yersinia effector and a Pseudomonas avirulence protein define a family of cysteine proteases functioning in bacterial pathogenesis," *Cell*, vol. 109, no. 5, pp. 575–588, 2002.

[174] E. E. Galyov, S. Hakansson, A. Forsberg, and H. Wolf-Watz, "A secreted protein kinase of *Yersinia pseudotuberculosis* is an indispensable virulence determinant," *Nature*, vol. 361, no. 6414, pp. 730–732, 1993.

[175] J. M. Dukuzumuremyi, R. Rosqvist, B. Hallberg, B. Åkerström, H. Wolf-Watz, and K. Schesser, "The Yersinia protein kinase A is a host factor inducible RhoA/Rac-binding virulence factor," *Journal of Biological Chemistry*, vol. 275, no. 45, pp. 35281–35290, 2000.

[176] S. J. Juris, A. E. Rudolph, D. Huddler, K. Orth, and J. E. Dixon, "A distinctive role for the Yersinia protein kinase:

actin binding, kinase activation, and cytoskeleton disruption," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 17, pp. 9431–9436, 2000.

[177] N. Sauvonnet, B. Pradet-Balade, J. A. Garcia-Sanz, and G. R. Cornelis, "Regulation of mRNA expression in macrophages after *Yersinia enterocolitica* infection," *Journal of Biological Chemistry*, vol. 277, no. 28, pp. 25133–25142, 2002.

[178] T. Yao, J. Mecsas, J. I. Healy, S. Falkow, and Y. H. Chien, "Suppression of T and B lymphocyte activation by a *Yersinia pseudotuberculosis* virulence factor, YopH," *Journal of Experimental Medicine*, vol. 190, no. 9, pp. 1343–1350, 1999.

[179] A. Alonso, N. Bottini, S. Bruckner et al., "Lck dephosphorylation at Tyr-394 and inhibition of T cell antigen receptor signaling by Yersinia Phosphatase YopH," *Journal of Biological Chemistry*, vol. 279, no. 6, pp. 4922–4928, 2004.

[180] K. Trülzsch, T. Sporleder, E. I. Igwe, H. Rüssmann, and J. Heesemann, "Contribution of the major secreted Yops of *Yersinia enterocolitica* O:8 to pathogenicity in the mouse infection model," *Infection and Immunity*, vol. 72, no. 9, pp. 5227–5234, 2004.

[181] A. Boland, M. P. Sory, M. Iriarte, C. Kerbourch, P. Wattiau, and G. R. Cornelis, "Status of YopM and YopN in the Yersinia Yop virulon: YopM of *Y. enterocolitica* is internalized inside the cytosol of PU5-1.8 macrophages by the YopB, D, N delivery apparatus," *EMBO Journal*, vol. 15, no. 19, pp. 5191–5201, 1996.

[182] G. Heusipp, K. M. Nelson, M. A. Schmidt, and V. L. Miller, "Regulation of htrA expression in *Yersinia enterocolitica*," *FEMS Microbiology Letters*, vol. 231, no. 2, pp. 227–235, 2004.

[183] M. Hentschke, L. Berneking, C. B. Campos, F. Buck, K. Ruckdeschel, and M. Aepfelbacher, "Yersinia virulence factor YopM induces sustained RSK activation by interfering with dephosphorylation," *PLoS ONE*, vol. 5, no. 10, Article ID e13165, 2010.

[184] M. W. McCoy, M. L. Marré, C. F. Lesser, and J. Mecsas, "The C-terminal tail of *Yersinia pseudotuberculosis* YopM is critical for interacting with RSK1 and for virulence," *Infection and Immunity*, vol. 78, no. 6, pp. 2584–2598, 2010.

[185] J. B. McPhee, P. Mena, and J. B. Bliska, "Delineation of regions of the Yersinia YopM protein required for interaction with the RSK1 and PRK2 host kinases and their requirement for interleukin-10 production and virulence," *Infection and Immunity*, vol. 78, no. 8, pp. 3529–3539, 2010.

[186] J. C. Haller, S. Carlson, K. J. Pederson, and D. E. Pierson, "A chromosomally encoded type III secretion pathway in *Yersinia enterocolitica* is important in virulence," *Molecular Microbiology*, vol. 36, no. 6, pp. 1436–1446, 2000.

[187] G. M. Young, M. J. Smith, S. A. Minnich, and V. L. Miller, "The *Yersinia enterocolitica* motility master regulatory operon, flhDC, is required for flagellin production, swimming motility, and swarming motility," *Journal of Bacteriology*, vol. 181, no. 9, pp. 2823–2833, 1999.

[188] S. Mildiner-Earley, V. L. Miller, and K. A. Walker, "Environmental stimuli affecting expression of the Ysa type three secretion locus," *Advances in Experimental Medicine and Biology*, vol. 603, pp. 211–216, 2007.

[189] K. A. Walker and V. L. Miller, "Regulation of the Ysa type III secretion system of *Yersinia enterocolitica* by YsaE/SycB and YsrS/YsrR," *Journal of Bacteriology*, vol. 186, no. 13, pp. 4056–4066, 2004.

[190] K. Venecia and G. M. Young, "Environmental regulation and virulence attributes of the Ysa type III secretion system of *Yersinia enterocolitica* biovar 1B," *Infection and Immunity*, vol. 73, no. 9, pp. 5961–5977, 2005.

[191] H. Matsumoto and G. M. Young, "Proteomic and functional analysis of the suite of Ysp proteins exported by the Ysa type III secretion system of *Yersinia enterocolitica* Biovar 1B," *Molecular Microbiology*, vol. 59, no. 2, pp. 689–706, 2006.

[192] D. H. Schmiel, G. M. Young, and V. L. Miller, "The *Yersinia enterocolitica* phospholipase gene yplA is part of the flagellar regulon," *Journal of Bacteriology*, vol. 182, no. 8, pp. 2314–2320, 2000.

[193] W. Zhang, S. Xu, J. Li, X. Shen, Y. Wang, and Z. Yuan, "Modulation of a thermoregulated type VI secretion system by ahl-dependent quorum sensing in *Yersinia pseudotuberculosis*," *Archives of Microbiology*, vol. 193, no. 5, pp. 351–363, 2011.

[194] F. Collyn, M. A. Léty, S. Nair et al., "*Yersinia pseudotuberculosis* harbors a type IV pilus gene cluster that contributes to pathogenicity," *Infection and Immunity*, vol. 70, no. 11, pp. 6196–6205, 2002.

[195] J. M. Balada-Llasat and J. Mecsas, "Yersinia has a tropism for B and T cell zones of lymph nodes that is independent of the type III secretion system.," *PLoS Pathogens*, vol. 2, no. 9, article e86, 2006.

[196] I. B. Autenrieth, P. Hantschmann, B. Heymer, and J. Heesemann, "Immunohistological characterization of the cellular immune response against *Yersinia enterocolitica* in mice: evidence for the involvement of T lymphocytes," *Immunobiology*, vol. 187, no. 1-2, pp. 1–16, 1993.

[197] P. H. Dube, P. A. Revell, D. D. Chaplin, R. G. Lorenz, and V. L. Miller, "A role for IL-1α in inducing pathologic inflammation during bacterial infection," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 19, pp. 10880–10885, 2001.

[198] S. A. Handley, P. H. Dube, P. A. Revell, and V. L. Miller, "Characterization of Oral *Yersinia enterocolitica* infection in three different strains of inbred mice," *Infection and Immunity*, vol. 72, no. 3, pp. 1645–1656, 2004.

[199] W. W. Lathem, S. D. Crosby, V. L. Miller, and W. E. Goldman, "Progression of primary pneumonic plague: a mouse model of infection, pathology, and bacterial transcriptional activity," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 49, pp. 17786–17791, 2005.

[200] J. M. Balada-Llasat, B. Panilaitis, D. Kaplan, and J. Mecsas, "Oral inoculation with Type III secretion mutants of *Yersinia pseudotuberculosis* provides protection from oral, intraperitoneal, or intranasal challenge with virulent Yersinia," *Vaccine*, vol. 25, no. 8, pp. 1526–1533, 2007.

[201] E. L. Hartland, A. M. Bordun, and R. M. Robins-Browne, "Contribution of YopB to virulence of *Yersinia enterocolitica*," *Infection and Immunity*, vol. 64, no. 6, pp. 2308–2314, 1996.

[202] T. Une and R. R. Brubaker, "In vivo comparison of avirulent Vwa- and Pgm- of Pst(r) phenotypes of Yersiniae," *Infection and Immunity*, vol. 43, no. 3, pp. 895–900, 1984.

[203] N. A. Okan, P. Mena, J. L. Benach, J. B. Bliska, and A. W. Karzai, "The smpB-ssrA mutant of Yersinia pestis functions as a live attenuated vaccine to protect mice against pulmonary plague infection," *Infection and Immunity*, vol. 78, no. 3, pp. 1284–1293, 2010.

[204] J. A. Rosenzweig, O. Jejelowo, J. Sha et al., "Progress on plague vaccine development," *Applied Microbiology and Biotechnology*, vol. 91, no. 2, pp. 265–286, 2011.

[205] H. Rüssmann, K. Panthel, B. Köhn et al., "Alternative endogenous protein processing via an autophagy-dependent pathway compensates for Yersinia-mediated inhibition of endosomal major histocompatibility complex class II antigen

presentation," *Infection and Immunity*, vol. 78, no. 12, pp. 5138–5150, 2010.

[206] A. Deuretzbacher, N. Czymmeck, R. Reimer et al., "β1 integrin-dependent engulfment of *Yersinia enterocolitica* by macrophages is coupled to the activation of autophagy and suppressed by type III protein secretion," *Journal of Immunology*, vol. 183, no. 9, pp. 5847–5860, 2009.

[207] K. Moreau, S. Lacas-Gervais, N. Fujita et al., "Autophagosomes can support *Yersinia pseudotuberculosis* replication in macrophages," *Cellular Microbiology*, vol. 12, no. 8, pp. 1108–1123, 2010.

[208] I. B. Autenrieth, A. Tingle, A. Reske-Kunz, and J. Heesemann, "T lymphocytes mediate protection against *Yersinia enterocolitica* in mice: characterization of murine T-cell clones specific for *Y. enterocolitica*," *Infection and Immunity*, vol. 60, no. 3, pp. 1140–1149, 1992.

[209] E. Bohn, E. Schmitt, C. Bielfeldt, A. Noll, R. Schulte, and I. B. Autenrieth, "Ambiguous role of interleukin-12 in *Yersinia enterocolitica* infection in susceptible and resistant mouse strains," *Infection and Immunity*, vol. 66, no. 5, pp. 2213–2220, 1998.

[210] E. Bohn, J. Heesemann, S. Ehlers, and I. B. Autenrieth, "Early gamma interferon mRNA expression is associated with resistance of mice against *Yersinia enterocolitica*," *Infection and Immunity*, vol. 62, no. 7, pp. 3027–3032, 1994.

[211] E. Bohn and I. B. Autenrieth, "IL-12 is essential for resistance against *Yersinia enterocolitica* by triggering IFN-γ production in NK cells and CD4+ T cells," *Journal of Immunology*, vol. 156, no. 4, pp. 1458–1468, 1996.

[212] I. B. Autenrieth and J. Heesemann, "In vivo neutralization of tumor necrosis factor-alpha and interferon-gamma abrogates resistance to *Yersinia enterocolitica* infection in mice," *Medical Microbiology and Immunology*, vol. 181, no. 6, pp. 333–338, 1992.

[213] S. E. Autenrieth, T.-R. Linzer, C. Hiller et al., "Immune evasion by *Yersinia enterocolitica*: differential targeting of dendritic cell subpopulations in vivo," *PLoS Pathogens*, vol. 6, no. 11, Article ID e1001212, 2010.

[214] E. M. Ribot, M. A. Fair, R. Gautom et al., "Standardization of pulsed-field gel electrophoresis protocols for the subtyping of Escherichia coli O157:H7, Salmonella, and Shigella for PulseNet," *Foodborne Pathogens and Disease*, vol. 3, no. 1, pp. 59–67, 2006.

[215] K. Asplund, T. Johansson, and A. Siitonen, "Evaluation of pulsed-field gel electrophoresis of genomic restriction fragments in the discrimination of *Yersinia enterocolitica* O:3," *Epidemiology and Infection*, vol. 121, no. 3, pp. 579–586, 1998.

[216] I. Iteman, A. Guiyoule, and E. Carniel, "Comparison of three molecular methods for typing and subtyping pathogenic *Yersinia enterocolitica* strains," *Journal of Medical Microbiology*, vol. 45, no. 1, pp. 48–56, 1996.

[217] H. Najdenski, I. Iteman, and E. Carniel, "Efficient subtyping of pathogenic *Yersinia enterocolitica* strains by pulsed-field gel electrophoresis," *Journal of Clinical Microbiology*, vol. 32, no. 12, pp. 2913–2920, 1994.

[218] P. Thoerner, C. I.B. Kingombe, K. Bögli-Stuber et al., "PCR detection of virulence genes in *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* and investigation of virulence gene distribution," *Applied and Environmental Microbiology*, vol. 69, no. 3, pp. 1810–1816, 2003.

[219] L. M. Sihvonen, S. Hallanvuo, K. Haukka, M. Skurnik, and A. Siitonen, "The ail gene is present in some *Yersinia enterocolitica* biotype 1A strains," *Foodborne Pathogens and Disease*, vol. 8, no. 3, pp. 455–457, 2011.

[220] R. Gierczyński, A. Golubov, H. Neubauer, J. N. Pham, and A. Rakin, "Development of multiple-locus variable-number tandem-repeat analysis for *Yersinia enterocolitica* subsp. palearctica and its application to bioserogroup 4/O3 subtyping," *Journal of Clinical Microbiology*, vol. 45, no. 8, pp. 2508–2515, 2007.

[221] L. M. Sihvonen, S. Toivonen, K. Haukka, M. Kuusi, M. Skurnik, and A. Siitonen, "Multilocus variable-number tandem-repeat analysis, pulsed-field gel electrophoresis, and antimicrobial susceptibility patterns in discrimination of sporadic and outbreak-related strains of *Yersinia enterocolitica*," *BMC Microbiology*, vol. 11, article 42, 2011.

[222] E. Palonen, M. Lindström, and H. Korkeala, "Adaptation of enteropathogenic Yersinia to low growth temperature," *Critical Reviews in Microbiology*, vol. 36, no. 1, pp. 54–67, 2010.

[223] A. Lawal, O. Jejelowo, A. K. Chopra, and J. A. Rosenzweig, "Ribonucleases and bacterial virulence," *Microbial Biotechnology*, vol. 4, no. 5, pp. 558–571, 2011.

[224] S. M. Tennant, N. A. Skinner, A. Joe, and R. M. Robins-Browne, "Homologues of insecticidal toxin complex genes in *Yersinia enterocolitica* biotype 1A and their contribution to virulence," *Infection and Immunity*, vol. 73, no. 10, pp. 6860–6867, 2005.

[225] R. H. ffrench-Constant, A. Dowling, and N. R. Waterfield, "Insecticidal toxins from Photorhabdus bacteria and their potential use in agriculture," *Toxicon*, vol. 49, no. 4, pp. 436–451, 2007.

[226] G. Bresolin, J. A. W. Morgan, D. Ilgen, S. Scherer, and T. M. Fuchs, "Low temperature-induced insecticidal activity of *Yersinia enterocolitica*," *Molecular Microbiology*, vol. 59, no. 2, pp. 503–512, 2006.

[227] M. C. Hares, S. J. Hinchliffe, P. C. R. Strong et al., "The *Yersinia pseudotuberculosis* and Yersinia pestis toxin complex is active against cultured mammalian cells," *Microbiology*, vol. 154, no. 11, pp. 3503–3517, 2008.

[228] G. Cornelis, "Distribution of beta-lactamases A and B in some groups of *Yersinia enterocolitica* and their role in resistance," *Journal of General Microbiology*, vol. 91, no. 2, pp. 391–402, 1975.

[229] G. Cornelis and E. P. Abraham, "Beta-lactamases from *Yersinia enterocolitica*," *Journal of General Microbiology*, vol. 87, no. 2, pp. 273–284, 1975.

[230] C. Long, T. F. Jones, D. J. Vugia et al., "*Yersinia pseudotuberculosis* and *Y. enterocolitica* infections, FoodNet, 1996–2007," *Emerging Infectious Diseases*, vol. 16, no. 3, pp. 566–567, 2010.

[231] W. Knapp, "Mesenteric adenitis due to *Pasteurella pseudotuberculosis* in young people," *The New England Journal of Medicine*, vol. 259, no. 16, pp. 776–778, 1958.

[232] J. R. Paff, D. A. Triplett, and T. N. Saari, "Clinical and laboratory aspects of *Yersinia pseudotuberculosis* infections, with a report of two cases," *American Journal of Clinical Pathology*, vol. 66, no. 1, pp. 101–110, 1976.