

# Current Perceptive on the Virulence Factors of *Yersinia Enterocolitica*: A Critical Review

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**Abstract** *Yersinia enterocolitica* is an important food-borne pathogen that has become more common in recent years because of the fecal oral transmission by humans and animals. After ingesting the contaminated food, this neglected pathogen begins its pathogenic activity by invading the digestive tract of the host. Due to its growth habits, low quantities in samples and physical similarities with other bacteria, *Y. enterocolitica* remains a challenge for the researchers and food handlers. We presented latest information on the virulence factor in this review. All *Yersinia enterocolitica* have an infection strategy that relies on a virulence factor to allow them to enter, adhering to, and colonize the host while evading the host defenses and avoiding host cell clearance.

**Keywords:** food borne, transmission, virulence factor, public health, *Yersinia*

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## 1. Introduction

Ingestion of bacteria or toxins contaminated food products is the most common cause of foodborne diseases worldwide. Foodborne diseases occur in sporadic and epidemic form resulting significant morbidity as well as mortality in the susceptible individuals [1]. *Yersinia enterocolitica* was discovered more than 60 years ago, but it was not widely recognized as a zoonotic pathogen until the late 1960s, when it was associated to foodborne gastrointestinal diseases [2]. Yersiniosis caused by *Y. enterocolitica* is the third most common foodborne disease in the European Union [3,4]. Globally, it is estimated that this foodborne bacterium is responsible for about 87000 cases annually [1]. *Yersinia* is a Gram-negative, non-spore-forming bacterium that belongs to the *Enterobacteriaceae* family, and it shares roughly 10%-30% DNA homology [5]. Based on biochemistry and serology, it has been divided into 6 biovars, 70 serotypes, and 3 species namely, *Y. enterocolitica*, *Y. pestis*, and *Y. pseudotuberculosis*. However, *Y. enterocolitica* is primarily responsible for foodborne infections in humans [6,7].

*Yersinia enterocolitica* infection is more common in countries with temperate climates rather than in tropical or subtropical regions. Bio-serotype 4/O: 3 predominate globally among *Y. enterocolitica*; and pigs are a major source of this bio-serotype [6]. *Yersinia enterocolitica* has more than 50 distinct serotypes (based on antigenic variations in cell wall lipopolysaccharide), and few of them are pathogenic [2]. Among many foodborne

microbes, *Yersinia enterocolitica* is an emerging versatile foodborne zoonotic pathogen that can result into high morbidity and mortality, especially in infants and young children [8]. The pathogen is important from public health as well as economic point of view [1].

All *Yersinia* species with the exception of *Y. pestis* are motile 22-30°C but not at 37°C. *Yersinia* develops at temperatures ranging from 0 to 45°C on non-selected and selective media, with an ideal temperature of 25-28°C [9]. The three human infections belonging to the genus *Yersinia* use virulence factors to effectively adhere to host cells/tissues and disrupt host cell function. *Yersinia pseudotuberculosis*, *Yersinia pestis*, and *Yersinia enterocolitica* are highly adapted psychrotrophic infections. *Yersinia pseudotuberculosis* and *Y. enterocolitica* cause self-limiting gastric infections. *Yersinia enterocolitica* is a recently evolved near identical subclone of *Y. pseudotuberculosis* [10]. Despite the fact that the causal agents of yersiniosis by *Y. enterocolitica* that causes gastroenteritis and extraintestinal infections, is a little-known infection [11]. Therefore, the virulence factor of *Y. enterocolitica* is not well addressed and a current review is an attempt to assess the recent understanding of virulence factor of *Yersinia enterocolitica*, an emerging foodborne pathogen.

### 1.1. Virulence Factors

The virulence factors identified in *Y. enterocolitica* are found on the chromosome and on a 70-Kb virulence plasmid known as pYV, which is only seen in virulent strains. These virulence features, particularly those encoded by plasmids, lead the invading *Y. enterocolitica*

infection and allow bacteria to persist inside the human host [12]. The virulence factors that allow *Y. enterocolitica* to survive in the host cell are listed below.

### 1.1.1. Flagella

It has been revealed that flagella and thus motility play a crucial role in commencing host cell invasion before *Y. enterocolitica* enters into close contact with the intestinal epithelium. Inactivation of the flagellar regulatory genes *flh DC* (the master regulatory component) or *fliA*, all of which are necessary for motility expression has been linked to a reduction in invasion comparable to that seen in strains within pYV inactivated. In line with these findings, when bacteria are brought into contact with an in vitro monolayer of eukaryotic cells by centrifugation, there is no difference in invasion between the flagellar mutants and the wild-type strain (despite the *inv* mutant's impaired invasion still being recognized) [13].

Distributions of shared and distinct virulence factors have a crucial influence in human infection routes types of infections and illness severity. In the pathogenesis of *Y. enterocolitica* and the development and progression of *Y. enterocolitica* both chromosomal and plasmid-derived virulence factors play a role. The presence of the 70-kb plasmid linked with *Yersinia* virulence pYV is required for YE pathogenicity [14].

### 1.1.2. Yersinia adhesion A protein (YadA)

It is critical for *Yersinia* to attach to the host cell surface and remain in close proximity during the delivery phase in order to efficiently transport *Yersinia* outer membrane proteins (Yop) into the host. YadA mediates mucus and epithelial cell adhesion and enhances host cell invasion when combined with invasins. YadA is a multi-functional surface-exposed virulence factor that confers the capacity to adhere to extracellular matrix proteins and is encoded on the pYV virulence plasmid [15]. The over expression of Yops (*Yersinia* outer membrane proteins) coincides with the induction of YadA expression. YadA is more important for virulence in YE than in YPT and it plays a key role in the positive control of both adherence to and invasion of host cells. YadA is only involved in a limited way in YPT providing solely an adhesive phenotype [15].

The primary adhesin responsible for *Yersinia* interaction with cells of the submucosa after crossing the intestinal epithelium is the virulence plasmid-encoded protein YadA. YadA expression is induced at or above 37°C and it is so plentiful that it can nearly coat the entire outer surface of the bacterial cell under these conditions. Surprisingly, despite its effectiveness and abundance YadA is not widely used. Due to a single nucleotide deletion, it results in a frame-shift mutation [16].

### 1.1.3. Lipopolysaccharide (LPS)

Gram-negative bacteria's outer membrane is primarily made up of LPS. It is made up of three parts: (i) lipid A, which is tethered to the membrane and linked to toxicity; (ii) the core which consists of both inner and outside moieties (mostly sugars); and (iii) the O antigen or O polysaccharide chain, which is the external component linked to antigenic characteristics. Nonetheless, as O antigen-deficient strains (serotypes O: 3 and O: 8) are

attenuated after oral infection of mice multiple investigations have revealed that the O antigen is involved in the colonization and invasion processes. In compared to wild-type strains these mutants colonize PP inefficiently and do not grow in the laboratory. In comparison to wild-type strains these mutants colonize PP inefficiently and do not grow in the spleen, liver or MLN. O antigen is essential for the appropriate production or function of other outer membrane virulence factors, which explains why Ysc internalization of the host cell is reduced [17].

### 1.1.4. Yersinia Type Three-secretion System (T3SS)

Those secreted by a T3SS are the most important virulence determinants in *Yersinia* and probably the most thoroughly researched (T3SS). All human pathogenic *Yersinia* species carry a 70-kb virulence plasmid to bypass host innate immunity and allow the disease to multiply and disseminate extracellularly. A group of genes on this plasmid is triggered by temperatures of 37°C in the presence of millimolar calcium concentrations, which are representative of the mammalian host. The T3SS 'nanochrome,' a hypodermic needle-like structure (the injectisome) and the translocon, which forms a channel across the host cell, are encoded by these genes [10].

### 1.1.5. Enterotoxin Yst

*Yersinia enterocolitica* has also been found to produce Yst a heat-stable chromosomally encoded enterotoxin. Several antigenically similar variations have been identified so far. However, the role of this toxin in diarrheal disease is largely unknown: (i) Yst is not detectable in diarrheal stool samples in experimental animal models after infection with *Y. enterocolitica*; (ii) some strains carry the *yst* gene but do not produce the enterotoxin, implying the presence of silent genes; and (iii) the proportions of enterotoxigenic bacteria are similar among bacteria. Non-invasive biotype 1A bacteria that cause diarrhea, on the other hand frequently carry a variant of the *yst* gene which could be the only virulence factor accounting for this diarrheal illness [18].

### 1.1.6. Invasin

Invasin is a chromosomally encoded protein that permits *Y. enterocolitica* and *Y. pseudotuberculosis* to attach to and enter host cells though it is a pseudogene in *Y. pestis* and hence, inactive. By binding to  $\beta 1$ -integrins on the surface of the host cell invasins promotes epithelial cell internalization in the small intestine. Integrins create clusters when invasins binds causing the cytoskeleton of the host cell to be altered.

This promotes phagocytosis which leads to bacteria internalization in epithelial cells. Invasin has a far greater affinity (up to 100 times stronger) for various integrins than its normal ligand fibronectin and these high interactions are what cause the disease. Effectiveness of internalization and Yop distribution into host cells [19].

### 1.1.7. High-Pathogenicity Island (HPI)

Another pathogenicity island, known as high pathogenicity Island, encodes virulence genes (HPI). This chromosomal region like the Ysa-PI site is only found in *Y. enterocolitica* biotype 1B. The HPI was classified as an iron-capture

island because most of the genes on the island are involved in the production transport and regulation of the siderophore *Yersinia* bactin [12].

### 1.1.8. *Y. pestis* Plasmid-specific Virulence Factors

Apart from the T3SS virulence plasmid two other plasmids specific to *Y. enterocolitica*, pPCP and pMT (also known as pFra) contain additional virulence components. Pla protease/adhesin is the plasminogen activator encoded by pPCP. Pla transforms plasminogen to plasmin, which subsequently destroys extracellular matrices and allows *Y. enterocolitica* to penetrate and move to lymphatic tissues quickly. Plasmin over-activation causes laminin and fibrin clot disintegration worsening migration across host barriers, which is exacerbated by Pla's adhesin and invasion activities [20].

### 1.1.9. Biovar 1A Strains

A review by Bhagat and Virdi provided experimental evidence for the presence of virulence factors for *Y. enterocolitica* biovar 1A. Strains belonging to biovar 1A are considered nonpathogenic because biovar 1A strains lack the pYV plasmid and the major chromosome determinants of virulence. The biovar 1A strains of *Y. enterocolitica* are distributed globally and have been isolated from asymptomatic and symptomatic individuals [21].

## 2. Concluding Remarks

A substantial amount of specific knowledge has developed over the previous three decades, allowing us to comprehend how *Yersinia enterocolitica* infiltrate tissues resist host defenses during infection. Despite the fact that *Yersinia* T3SS is likely the most well studied of its kind, many questions remain unresolved. For example, thoroughly understanding the function of YopM, as well as the global molecular mechanisms that support the regulatory interactions that must exist between the T3SS system and the adhesions will be a significant step forward. It is also crucial to try to figure out how the transmission works. Finally, there is a need to better understand how *Yersinia* virulence factors penetrate the host cells and cause infection. Some of these virulence factors have not been thoroughly investigated. Therefore, further comprehensive and systematic studies are needed to elucidate the virulence factor of *Y. enterocolitica* that has emerged an important pathogen of food safety concern.

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## Contribution of Authors

All the authors contributed equally. They read the final version, and approved it for the publication.

## Conflict of Interest

The authors declare that they do not have conflict of interest.

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