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Clinically important *Yersinia*: Review study of Disease, Virulence and Antibiotic resistance

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Abstract

Yersinia spp. is an enterobacteria that causes a prominent zoonotic diseases. Plague, Yersinosis, Far-East Scarlett-Like Fever and Kawasaki Disease were a common recorded diseases. While Yersinia genus compile 18 species, only three were clinically important human pathogens: *Y. pseudotuberculosis*, *Y. pestis* and *Y. enterocolitica*. Serotyping is common among *Yersinia* and used to distinguish between pathogenic and non-pathogenic species. Clinical symptoms ranged from high fever (up to 39 to 40°C), malaise, chills, and headache in Plaque to gastrointestinal symptoms usually resolve within 2 to 3 weeks. The complications may include, erythema nodosum, arthritis, Reiter's disease and glomerulonephritis, can occur. *Y. enterocolitica* and *Y. pseudotuberculosis* may associate with mesenteric lymphadenitis, terminal ileitis, pseudo-appendicitis and sepsis. Manipulation of Yersinia may require biosafety level 3 laboratory and all immunological, and molecular assay targeting F1 antigen for diagnosis. Yersinia have arrays of virulence factors includes: Ypm (responsible for superantigen symptoms), pYV(plasimd who carry set of virulence genes: Yops, outermwmbrane proteins; YadA, an adhesin who binds to collagen and laminin and eliciting inlafamatiry respones), HPI (The high-pathogenicity island which carry: Psn, an receptor for the siderophore; irp1 and irp2 which encode high-molecular-weight proteins involved in synthesis of yersiniabactin) and Yersinia Chromosomal Virulence Factors (YCVF):(i) invA, encoding an invasin, (ii) ail, encoding a protein that mediates adhesion and invasion into host cells, and (iii) ystA or ystB, encoding enterotoxins that cause fluid accumulation in the intestines. The drug of choice are Streptomycin and gentamicin while many MDR isolates were reported worldwide and there is an relation between resistance style and serotypes of Yersinia. The current review conclude importance of Yersinia spp. as a zoonotic pathogen equipped with group of virulence traits and resistance to antibiotics that may push a real threat for infected person.

Keywords: *Yesinia spp., Plaque, Yersinosis, Kawasaki Disease, pYV, YPM*

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Introduction

The genus Yersinia is gram-negative and belongs to the family of Enterobacteriaceae. The genus *Yersinia* includes 18 species (*Y. aldovae, Y. aleksiciae, Y. bercovieri, Y. enterocolitica, Y. entomophaga, Y. frederiksenii, Y. intermedia, Y. kristensenii, Y. massiliensis, Y. mollaretii, Y. nurmii, Y. pekkanenii,Y. pseudotuberculosis, Y. pestis, Y. rohdei, Y. ruckeri, Y. similis, and Y. wautersii*), of which *Y. pseudotuberculosis, Y. pestis* and *Y. enterocolitica* are pathogenic, but as *Y. pestis* is effectively a clone of *Y. pseudotuberculosis* , there are currently only two full species that are of clinical significance. The other species are commonly found in soil and water, and generally not pathogenic [1-5]. *Yersinia* are facultatively anaerobic, oxidase negative, and catalase-positive, and they do not form spores. The optimum growth temperature of *Yersinia* is 28-29°C and their growth range is 4-42°C, but *Y. enterocolitica* and *Y. pseudotuberculosis* can grow at temperatures near 0°C[6,7].

It is interesting that *Y. pseudotuberculosis* and *Y. enterocolitica* are among the most divergent of the species, and are now thought to have gained pathogenicity independently, although they cause similar gastrointestinal diseases in humans and also in animals. They also share pathogenicity islands and other virulence factors, now proposed to have been gained independently, presumably initially from other genera, but perhaps reaching the second species by transfer within the genus [8]. *Y. pseudotuberculosis* and *Y. enterocolitica* are enteropathogenic, while *Y. pestis* is the causative agent of plague. *Y. pseudotuberculosis* and *Y. pestis* are genetically highly similar and *Y. pestis* probably emerged from *Y. pseudotuberculosis* [9]. As genome sequences became available, many isolates first typed as Y. pseudotuberculosis were reclassified into other species that are now included in a group known as the '*Y. pseudotuberculosis* complex'. The species include *Y. pseudotuberculosis / Y. pestis, Y. similis* [10,11]. *Y. enterocolitica* is well known as a cause of yersiniosis in children. This microorganism is ubiquitous in nature and has been isolated from different types of foods, animals, and environments [12]. Although, numerous *Y. enterocolitica* biotypes have been isolated from nature, only a few are human pathogens [13]. The current review study intended to highlighted the diseases, virulence factors and antibiotic resistance of *Yersinia* spp.

Yersinia pestis

Yersinia pestis, etiologic agent of plague, is one of the most successful zoonotic pathogens known. Molecular investigations have revealed that *Y. pestis* spread multiple times from its original foci in Central Asia to cause three recognized pandemics: Justinian's plague in the 6th– 7th centuries, medieval plague in the 14th– 17th centuries (including the Black Death), and the third pandemic, which began ~1855 in the Chinese province of Yünnan. *Y. pestis* remains a human health threat due to the severity of the disease, the many established natural plague foci, and its potential for use as a bioterror agent [14,15]. Fleas transmit *Y. pestis* from infected domestic rats to humans causing bubonic plague. *Y. pestis* also can be transmitted via respiratory secretions following contact with another infected human, leading to pneumonic plague. Currently, plague is still a public health threat in certain regions of Asia, Africa, North and South America. Because plague is highly contagious, *Y. pestis* can be used in biological warfare and is considered a Category A agent of bioterrorism [16].

Yersinia pestis isolates carry genes for the O:1b serotype, suggesting that it emerged from a *Y. pseudotuberculosis* O:1b progenitor [17]. However, in *Y. pestis*, four O-antigen genes have inactivating mutations, and an O antigen is not produced. Interestingly, genes specific to many of the *Y. pseudotuberculosis* O-antigen serotypes were identified in other species in the *Y. pseudotuberculosis* complex, which led to the proposal that the O-antigen serotyping scheme should apply to all members of this complex [18].

Yersinia pseudotuberculosis

It was first isolated in 1883 from tuberculosis-like lesions in guinea pigs. *Yersinia pseudotuberculosis* is a fecal-oral pathogen adept at contaminating chilled food stores due to the organisms ability to proliferate at temperatures as low as 4°C. *Y. pseudotuberculosis* is generally considered an enteric pathogen, but it has also been associated with other medical complications such as arthritis, erythema nodosum, desquamation, rash, pneumonia and nephritis. Yersiniosis caused by *Y. pseudotuberculosis* is often acquired through the ingestion of contaminated food, but zoonotic transmission is possible, and outbreaks have been reported in Finland, Russia and Japan [19,20]. Serotyping is a common *Y pseudotuberculosis* typing method, dividing *Y pseudotuberculosis* into 15 O-serotypes (O:1–O:15) and 10 subtypes (O:1a–O:1c, O2a–O2c, O:4a–O:4b, and O:5a–O5:b) based on variability in lipopolysaccharide O-antigen profiles. Most European *Y pseudotuberculosis* isolates are of serotypes O:1–O:3, whereas serotypes O:4–O:15 are primarily found in Asia. All *Y pseudotuberculosis* strains are considered potentially pathogenic, but only *Y pseudotuberculosis* serotypes O:1–O:6 and O:15 have been clinically isolated. The most common clinical serotypes are O:1a, O:1b, and O:3 in Europe and O:4b and O:5b in the Far East. Serotypes O:7–O:14 have only been isolated from environmental and animal sources in Asia. *Y pseudotuberculosis* can be assigned into 6 genetic groups (G1–G6) based on the presence of 3 key virulence factors: the *Y pseudotuberculosis*virulence plasmid (pYV), the high pathogenicity island (HPI), and the subtype of *Y pseudotuberculosis*-derived mitogen produced (YPMa/YPMb/YPMc). Interestingly, expression of the O-antigen component of the *Y. pseudotuberculosis* LPS is downregulated at 37°C, and this is also true for other *Yersinia* species. However, the O antigen is required for virulence, as well as for protection against antimicrobial chemokines such as polymyxin B. Thus, downregulation may be delayed until the later stages of infection [21,22].

Yersinia enterocolitica

Yersinia enterocolitica includes nonpathogenic biotype 1A and pathogenic biotypes 1B, 2, 3, 4, and 5 [23]. Pigs are the main reservoirs and vehicles for *Y. enterocolitica* transmission, but virulent strains have been also detected in milk and dairy products. Classification of *Y. enterocolitica strains* into biotypes or serotypes (or bioserotypes) is based on biochemical tests and the somatic O antigen (lipopolysaccharide or LPS), with six biotypes (1A, 1B, 2, 3, 4, and 5) and more than 57 serotypes. Nonetheless, most of the strains belong to biotypes 2, 3, and 4 and to serotypes O:3, O:5,27, O:8, and O:9. Y. enterocolitica is subdivided into the Y. enterocolitica subspecies enterocolitica, which includes mainly biotype 1B, and the *Y. enterocolitica* subspecies palearctica, which includes the remaining biotypes [24].

Clinical Symptoms of Yersinial Infections:

The first symptoms of plague are similar to those of the flu, with high fever (up to 39 to 40°C), malaise, chills, and headache. An important clue for suspecting plague is contact history with wild animals in natural plague foci or with other plague patients. If a patient develops sudden high fever after close contact with dead animals (rodents or other wild animals) in a region where plague is endemic, bubonic plague (with regional lymph node swelling), pneumonic plague (with severe coughing and pneumonic signs by X ray), or septicemic plague (with sudden high fever and chills) should be highly suspected. The incubation period is generally 2 to 3 days but may be as long as 6 days. If the patient is infected by inhaling a large quantity of Y. pestis, causing primary pneumonic plague, the incubation period might be 1 day or less, and the symptoms and signs may progress very quickly. In cases of bubonic plague, patients usually develop regional red, dry, and hot skin, with progressive severe pain in the flea-biting region and forced position caused by severe pain of the swollen lymph nodes [25,26].

Yersiniosis, which is caused by the enteric bacterial pathogens Yersinia enterocolitica and Yersinia pseudotuberculosis, was the third most commonly reported zoonotic infection in Europe in 2015 [27]. Transmission from animals to humans can occur via direct contact with animals or their environment, although most human gastrointestinal infections are foodborne. Outbreaks of yersiniosis associated with the consumption of contaminated meat and dairy products, and more recently salad vegetables, have been documented in the literature. Gastrointestinal symptoms usually resolve within 2 to 3 weeks without recourse to antibiotics, but secondary immunological complications, including erythema nodosum, arthritis, Reiter's disease and glomerulonephritis, can occur. Furthermore, *Y. enterocolitica* and *Y. pseudotuberculosis* are also associated with causing a number of other primary acute infections, including mesenteric lymphadenitis, terminal ileitis, pseudo-appendicitis and sepsis. Infection with Y. pseudotuberculosis causes acute abdominal pain and diarrhea. In immunocompromised persons or persons with underlying diseases, systemic infections are possible [28]. Diseases caused by superantigenic toxin-producing bacteria share clinical features such as the following: high-grade fever, conjunctival inflammation, pharyngeal inflammation, and latent development of an erythematous skin rash followed by desquamation in the convalescent phase. Superantigens have been shown to enhance susceptibility to lipopolysaccharide-induced shock [29,30].

Laboratory Diagnosis:

The gold standard for plague diagnosis in the laboratory is the isolation and identification of the plague pathogen from clinical specimens. The pathogen can be cultivated on many routinely used media, including brain heart infusion broth, MacConkey agar, and sheep blood agar. Y. pestis grows optimally at 26 to 28°C; however, incubation at 37°C is necessary for F1 antigen production. The colonies formed on the agar plate after a 48-h incubation are small (about 1 to 2 mm in diameter), with raised centers and a flat periphery. Y. pestis appears as small pleomorphic rods by Gram staining and bipolar coccobacilli by Giemsa or Wayson staining. The cultures could be specifically lysed by Y. pestis phage at 22 to 25°C. Y. pestis is not active in terms of biochemical assays; therefore, conventional biochemical identification systems sometimes result in misidentification with Y. pseudotuberculosis or other enterobacteria Isolation of Y. pestis should be performed at minimum in a biosafety level 3 laboratory [31].

F1 antigen is typically used as a target to detect Y. pestis by immunological methods. A passive hemagglutination test and F1 antigen hemagglutination inhibition test are conventionally employed for detecting F1 antigen. However, direct fluorescent antibody testing and enzyme-linked immunosorbent assays have also been reported for detecting F1 antibody or F1 antigen quantitatively. Y. pestis can be detected by PCR targeting the F1 antigen gene (caf1), pla gene, or chromosomal fragments (such as fragment 3a). However, the pla gene and chromosomal fragment targets were recently shown to be unreliable for detecting Y. pestis. Immunological and nucleic acid-based detection of Y. pestis can be performed in a biosafety level 2 laboratory. For areas without a supporting laboratory to perform the above-described bacterial isolation, identification, and immunological or molecular detection assays, point-of-care testing will be helpful[32,33].

Immunochromatographic assays (ICA) have been employed for rapid on-site detection. The colloidal gold-based ICA can meet the urgent need for on-site detection in remote centers; however, it must be conducted by well-trained professionals to ensure the accuracy of the results. An up-converting phosphor technology-based ICA has been developed with advantages of reliability, quantification, and robustness. Portable real-time quantitative PCR may also be applied to detect plague pathogen in the field [34,35].

Diseases:

The arrays of diseases implicated to Yersinia spp. can be summarized below:

1-Plaque:

Three major forms of plague are usually described, including bubonic, pneumonic, and septicemic plague. However, Y. pestis can be transmitted not only by flea bites (causing bubonic plague) and respiratory

droplets (causing pneumonic plague), but also by the consumption of uncooked contaminated meat (causing gastrointestinal plague) and contact with infected pets/domestic animals (causing conjunctivitis, skin plague, or pneumonic plague). In addition, plague pharyngitis, meningitis, and endophthalmitis have been reported, albeit rarely. If bubonic plague is not recognized and treated in time, it can develop into pneumonic plague or systemic plague (septicemic plague) by spreading Y. pestis via blood; this plague type has a very high mortality rate. Septicemic plague can also be caused directly by blood infection of the pathogen through a cut [36,37].

2-Children Yersinosis:

The term "*Y. enterocolitica and Y. pseudotuberculosis* infections" or "yersiniosis" is applied for two infectious diseases caused by Yersinia. These are pseudotuberculosis and intestinal yersiniosis followed by intoxication, injuries to the gastrointestinal tract and multiple organ disorders in case of miscellaneous and multi-disorder disease types. According to course duration of the disease it is classified as an acute (lasts for one month), a protracted (no longer than 3 months) and a chronic form (longer than six months). Concern the virulence traits many studies stated that , YPM genes (the superantigen Y. pseudotuberculosis-derived mitogen) and responsible for the typical pseudotuberculosis symptoms (rash, skin desquamation, red tongue) [38].

3- Far- East Scarlett- Like Fever:

Far East Scarlett-like Fever (FESLF), is manifested via fever, rash and injury of liver and joints and maily caused by *Yersinia pseudotuberculosis*. The mainly implicated virulence factor is superantigen *Y pseudotuberculosis*-derived mitogen A (YPMa) [39,40].

4- Kawasaki Disease

Kawasaki disease (KD), a febrile vasculitis of unknown origin, can cause coronary artery dilation and is increasing in incidence worldwide. The etiology of Kawasaki disease (KD) is unknown. Reportedly, there is an association between KD and *Yersinia pseudotuberculosis*. It is an enteric pathogen, causes a variety of clinical symptoms such as fever, rash, desquamation, strawberry tongue, lymphadenopathy, and conjunctivitis that sometimes satisfy the clinical criteria for KD. Some research groups have reported an association between YPT and KD [41-44].

Virulence Factors:

1- *Y. pseudotuberculosis*-derived Mitogen (YPM):

Concern the virulence traits many studies stated that , YPM genes (the superantigen Y. pseudotuberculosis-derived mitogen) and responsible for the typical pseudotuberculosis symptoms (rash, skin desquamation, red tongue). Bacterial superantigens (SAgs) are immunostimulatory toxins that induce acute diseases mainly through the massive release of inflammatory cytokines. Yersinia pseudotuberculosis is the only Gram-negative bacterium known to produce a SAg (Y. pseudotuberculosis-derived mitogen [YPM]). This SAg binds major histocompatibility complex class II molecules on antigen-presenting cells and T cell receptors (TcR) and can activates a potentially hepatotoxic CD4+ T cell population[45]. The YPM is the only superantigenic toxin identified in Gram-negative bacteria. Superantigens are also produced by *Staphylococcus aureus*, *Staphylococcus pyrogenes*, and some retroviruses. Three YPM variants have been detected: YPMa, YPMb, and YPMc, encoded by chromosomal genes of the same name (*ypmA*, *ypmB*, and *ypmC*). The term "superantigen" refers to YPMa possessing 3 additional properties, in addition to those of a conventional antigen: (1) YPMa is able to bind directly to major histocompatibility complex (MHC) class II molecules on antigen presenting cells; (2) YPMa has a

specificity for a set of Vβ elements, the variable region on the beta chain of a T-cell receptor, and this interaction is independent of antigen specificity; and (3) YPMa is able to activate T cells, which are CD4+ or CD8+, including T cells from donors with different MHC class II allotypes [46].

2- *Y. pseudotuberculosis* virulence plasmid (pYV)

The presence of the pYV is requisite for pathogenicity in *Yersinia* species; therefore, the presence or absence of this plasmid divides strains into pathogenic (G1–G3, G5–G6) and nonpathogenic subgroups (G4). Subgroups G2 and G3 comprise the majority of clinical isolates, and subgroups G1, G2, and G6 comprise the minority.The major virulence factors encoded by pYV are a type III secretion system and effector proteins termed *Yersinia* outer proteins (Yops). The YopE is a GTPase-activating protein, and YopH is a protein tyrosine phosphatase, both of which are antiphagocytic. The YopO/YpkA is a serine threonine kinase. The YopM can transit to the host cell nucleus. The YopJ/P inhibits the production of proinflammatory cytokine tumor necrosis factor-α (TNF-α) and induces macrophage apoptosis. The YopT is a cytotoxin that causes actin filament disruption. All Yops have additionally been shown to disrupt intracellular signaling or result in cytoskeletal changes that interfere with phagocytosis [47,48]. The pYV also encodes proteins involved in the control and translocation of the effector Yops to the target cell: YopN, YopB, YopD, TyeA, lcrG, and lcrV. Pathogenic *Yersinia* species preferentially target the cells of the innate immune system (neutrophils, macrophages, and dendritic cells) for injection of Yops, attenuating the innate immune response [49]. YadA is an adhesin encodes by plasmid gene carred on pYV . YadA binds collagen I, II, IV, and laminin, and the interactions between YadA and collagen may contribute to chronic Y. enterocolitica infections, such as reactive arthritis. YadA supports the creation of densely packed microcolonies of Yersinia in three-dimensional collagen gels [50]. YadA also elicits an inflammatory response in epithelial cells by inducing the production of interleukin-8 (IL-8), which is mediated by mitogen-activated protein kinase (MAPK), and by contributing to the intestinal inflammatory cascade. Additionally, YadA mediates cell adhesion and host cell responses induction, like cytokine production, autoagglutination, and serum resistance. YadA also plays a central role in promoting serum resistance. showed that YadA acted as C4-binding protein (C4bp) receptors, and binding of C4bp could help Y. enterocolitica to evade complement-mediated clearance in the human host [51,52].

3- High Pathogenicity Island (HPI)

The HPI is a 36-kb chromosomal DNA fragment that carries the biosynthetic gene cluster for yersiniabactin, a molecule involved in siderophore-mediated iron acquisition. Iron uptake is a prerequisite for successful bacterial growth and dissemination. The presence of HPI and yersiniabactin production has been shown to increase virulence [53]. The high-pathogenicity island (HPI) is closely associated with symptoms of Y. pseudotuberculosis yersiniosis. The HPI encodes proteins that are involved in the biosynthesis, regulation, and transport of the siderophore yersiniabactin. For that reason, the HPI has been referred to as an “iron capture island.” There are five genes within the island (*psn*, *irp1*, *irp2*, *ybtP*, and *ybtQ*) that are involved in the yersiniabactin system. Psn is the outer membrane receptor for the siderophore. The genes *irp1* and *irp2* encode high-molecular-weight proteins involved in the nonribosomal synthesis of yersiniabactin. *irp2* is a marker of high pathogenicity and is found only in pathogenic strains [54,55].

4- Yersinia Chromosomal Virulence Factors (YCVF):

The chromosomal virulence genes include (i) invA, encoding a protein that targets host cell surface receptors, which promotes phagocytosis of the bacteria into the cell, (ii) ail, encoding a protein that mediates adhesion and invasion into host cells, and (iii) ystA or ystB, encoding enterotoxins that cause fluid

accumulation in the intestines. Virulent strains carry virulence genes ystA, invA and ail, whilst less virulent strains carry ystB [56,57]. Some studies showed that in an early phase of Y. enterocolitica infection, InvA is required for effective bacteria translocation into M cells and Peyer's patches colonization . InvA binds to integrins, which leads to the creation of integrin clusters, triggers remodeling of the actin cytoskeleton and leads to the internalization of Y. enterocolitica to epithelial cells. The above is known as the "zipper" invasion mechanism, and internalization allows the delivery of Yops to host cells [58,59].

Treatment:

Y. pestis isolates worldwide are sensitive to streptomycin; however, a multidrug-resistant (MDR) strain was isolated from Madagascar. Fortunately, this MDR strain has never emerged again naturally in this region and other parts of the world. There is a concern that this MDR strain (resistant to streptomycin, chloramphenicol, ampicillin, spectinomycin, kanamycin, tetracycline, sulfonamides, and minocycline) may be attractive to bioterrorists who may want to perpetuate a bioterrorism attack using this strain. If infection by such a strain does occur, caution must be used in the selection of effective antibiotics by avoiding administration of the above-mentioned ones. The majority of human cases can be treated successfully with effective antibiotics according to the United States Centers for Disease Control and Prevention (CDC)'s recommendation. Streptomycin and gentamicin are recommended for adult patients, including immunocompromised patients and pregnant women. Streptomycin and gentamicin may also be administered in children; however, the dosage should be reduced. Alternatively, the combination of doxycycline, ciprofloxacin, and chloramphenicol could also be used for both adults and children [60,61].

Antimicrobial therapy is not usually recommended for treating enterocolitis in immunocompetent hosts since most of the gastrointestinal infections are self-limiting. However, immunocompromised patients with invasive infection, who are at increased risk for developing bacteremia or even septicemia, need special attention and antibiotic treatment since the mortality rate in these cases can be as high as 50% [62]. According to the common profile of susceptibility among Y. enterocolitica strains the initial recommendations for antimicrobial chemotherapy from public institutions, such as the WHO, included tetracycline, chloramphenicol, gentamicin, and cotrimoxazole. However, other compounds such as ciprofloxacin, ceftriaxone, and cefotaxime are also considered since they have shown excellent in vitro activity and have been successfully used to treat complicated infections (liver abscess, endocarditis, and septicemia) [63,64].

Antibiotic Resistance and Serotypes

The resistance profiles to different antimicrobial agents have been examined among strains collected from animal and environmental reservoirs, meat products, as well as those recovered from the clinical setting. Heterogeneity of the antimicrobial resistance pattern is shown to be depending on the bioserotype and geographical distribution. The levels of resistance to β-lactams, which are the major family of antibiotics currently used, have been extensively studied in strains of both animal and human origin. In general terms, high percentages of resistance to ampicillin are detected: values >85% resistance have been reported for non-clinical strains and >95% in the case of clinical isolates. Nonetheless, lower rates of resistance have been reported (13–57.1%) for strains obtained from the animal and, to a lesser extent from the human, setting[65-68].

In the case of amoxicillin/clavulanic acid, heterogeneous susceptibility profiles have been seen among Y. enterocolitica strains. High levels of resistance (100% for non-clinical strains and >75% for clinical isolates) have been shown to occur in strains belonging to biotypes 1A, 2, and 3 collected from around the world, including serotype O:5,27 strains from Canada (presumably related to biotypes 2 or 3 according to

the most prevalent biotype-serotype associations). However, reported very low levels of resistance (<3%) for strains serotyped as O:5 and O:9 (putatively belonging to biotypes 2 or 3) obtained from animals in the United States. On the other hand, bioserotype 4/O:3 consistently shows the lowest resistance values, <10%, among all the isolates regardless of the country of isolation. Similar to the resistance levels observed for ampicillin, most of the Y. enterocolitica strains are also resistant to cefalothin, a first-generation cephalosporin. Several studies have reported percentages of resistance >85% in strains of animal origin and >98% in strains isolated from humans [69].

Fortunately, most of the strains studied remain susceptible to more recent cephalosporins, including the second-generation compound cefuroxime and third-generation cephalosporins such as ceftriaxone, ceftazidime, and cefotaxime. Similarly, a more recent study conducted in Switzerland showed that all bioserotype 4/O:3 clinical isolates were susceptible, while higher resistance rates were observed for biotype 1A (45%) and bioserotypes 2/O:5,27, 2/O:9, and 3/O:3 (>80%) [70]. Information regarding imipenem resistance is also scarce. To our knowledge, only one study from Greece has been conducted, showing 8% of the strains of animal origin to be resistant to this drug. With respect to clinical isolates, no resistance to imipenem has been reported. Other antimicrobials which deserve to be highlighted are those belonging to the group of aminoglycosides. Full susceptibility to kanamycin and gentamicin has been reported in almost all studies regardless of the source of isolation [71]. Higher heterogeneity has been observed for streptomycin among clinical and non-clinical strains. Several studies have revealed a lack of resistance, particularly concerning biotype 2 strains, while others have reported levels of resistance ranging from 5.6% to 28.6%. The highest levels of resistance to streptomycin have been described for strains belonging to bioserotype 4/O:3. Among strains of animal origin, studies carried out in Italy and Germany showed percentages of resistance of 64% and 75%, respectively. In the clinical setting, strains isolated in Spanish hospitals have reported the highest levels of resistance to streptomycin (≥90%); whereas the remaining studies, also performed in Europe, show a prevalence of resistance <30%. Cases in which high levels of resistance have been reported are attributed to horizontal transfer of plasmids carrying genes which confer resistance to streptomycin [72,73].

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