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ARTICLE

Yersinia enterocolitica strains associated with human infections in Switzerland 2001–2010

M. Fredriksson-Ahomaa · N. Cernela · H. Hächler · R. Stephan

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Abstract *Yersinia enterocolitica* infections are common in humans. However, very scarce data are available on the different biotypes and virulence factors of human strains, which has proved to be problematic to assess the clinical significance of the isolated strains. In this study, the presence of the *ail* gene and distribution of different bio- and serotypes among human *Y. enterocolitica* strains and their possible relation to the genotype and antimicrobial resistance were studied. In total, 128 *Y. enterocolitica* strains isolated from human clinical samples in Switzerland during 2001–2010 were characterised. Most (75 out of 128) of the *Y. enterocolitica* strains belonged to biotypes 2, 3 or 4 and carried the *ail* gene. One of the 51 strains that belonged to biotype 1A was also *ail* positive. Most of the *ail*-positive strains belonged to bioserotype 4/O:3 (47 out of 76) followed by 2/O:9 (22 out of 76). Strains of bioserotype 4/O:3 were dominant among patients between 20 and 40 years old and strains of biotype 1A dominate in patients over 40 years. Strains belonging to biotypes 2, 3 and 4, which all carried the *ail* gene, exhibited a high homogeneity with PFGE typing. *Y. enterocolitica* 2/O:5,27 and 2/O:9 strains showed resistance to amoxicillin/clavulanic acid and cefoxitin, but *Y. enterocolitica* 4/O:3 strains did not.

M. Fredriksson-Ahomaa
Department of Food Hygiene and Environmental Health, Faculty of Veterinary Medicine, University of Helsinki, Helsinki, Finland

N. Cernela · H. Hächler · R. Stephan (✉)
Institute for Food Safety and Hygiene, Vetsuisse Faculty, University of Zurich,
Winterthurerstrasse 272,
8057 Zurich, Switzerland
e-mail: stephanr@fsafety.uzh.ch

Introduction

Yersiniosis is a zoonotic bacterial disease with high public health relevance, especially in Europe because of its high incidence [1]. It is the third most frequently reported bacterial enteric disease after campylobacteriosis and salmonellosis in most European countries [2]. Human illness is mainly caused by *Yersinia enterocolitica*, which includes strains of diverse pathogenicity. *Y. enterocolitica* strains belonging to biotypes 1B and 2–5 are considered pathogenic, whereas strains belonging to biotype 1A are in general considered non-pathogenic. Pathogenicity can also be determined by PCR methods detecting different virulence genes [3]. Further characterisation of pathogenic *Y. enterocolitica* strains is still frequently determined by pulsed-field gel electrophoresis (PFGE). The PFGE types have been shown to correlate with biotype [4].

Y. enterocolitica is considered to be an important food-borne pathogen. Infection is most often acquired by eating raw or undercooked pork [3]. Rarely, this organism is transmitted through contaminated blood during a transfusion. Common symptoms of food-borne infections are diarrhoea, abdominal pain and fever, but sequelae, such as joint pain (reactive arthritis) and skin rash (erythema nodosus), are not uncommon [1, 5]. Infection with *Y. enterocolitica* occurs most often in young children [2].

Uncomplicated yersiniosis usually resolves on its own without antimicrobial treatment. However, in more severe cases, like septicaemia or focal extra-intestinal infection, and in immune-compromised patients, medication may be required. *Y. enterocolitica* is a β-lactamase producer and thus is resistant to ampicillin and first-generation cephalosporins, but it is mostly susceptible to other antimicrobials, such as aminoglycosides, tetracyclines, trimethoprim-sulfamethoxazole and fluoroquinolones, that are used for

therapy. Multi-drug-resistant strains, which are resistant to streptomycin, sulfonamides, tetracycline and /or nalidixic acid, have occasionally been reported among some *Y. enterocolitica* strains [6].

The most commonly reported serotype of *Y. enterocolitica* strains isolated from human cases in Europe is O:3 and less commonly O:9 [2]. However, very scarce data on the virulence genes and the distribution of different biotypes among human strains are available. In this study, human *Y. enterocolitica* strains isolated during 2001 to 2010 in Switzerland were characterised to obtain information about the *ail* gene, and bio- and serotypes present in human clinical strains. Furthermore, the strains were genotyped and the antimicrobial resistance was studied.

Materials and methods

In total, 128 *Y. enterocolitica* strains collected from human patients in Switzerland during 2001 to 2010 were characterised (Table 1). Most of the strains (94%) were from humans suffering from diarrhoea, 4 strains were from blood, 2 from liver, 1 each from gall bladder, ulcer and abscess. *Y. enterocolitica* strains were almost equal in number in female (62) and male (63) patients. Only 6 strains (5%) were from patients under 6 years of age, but 28 strains (22%) were from patients over 60 (Table 1). Six patients reported having travelled abroad before infection.

All 128 *Y. enterocolitica* strains were biotyped and serotyped. The biotype was determined using pyrazinamidase and tween activity, esculin hydrolysis, indole production, and salicin, xylose and trehalose fermentation [4]. Serotyping was carried out with slide agglutination using commercial *Y. enterocolitica* O:3, O:5, O:9 and O:27 antisera (Sifin, Berlin, Germany). PCR was used to detect the *ail* gene located in the chromosome of pathogenic *Y. enterocolitica* strains according to Thoerner et al. [7].

All strains were genotyped with pulsed field gel electrophoresis (PFGE) according to the PulseNet protocol (http://www.cdc.gov/pulsenet/protocols/yersinia_Apr2006.pdf) using restriction enzyme *XbaI* (New England Biolabs, Beverly, MA). DNA fragments were separated with a CHEF-DR III system (Bio-Rad, Hercules, CA, USA) using pulse times ranging from 5 to 40 s for 19 h at an angle of 120°C. *Salmonella enterica* serovar Braenderup H9812 (New England Biolabs) was used as the standard. GelCompar II software (Applied Maths NV, Sint–Martens–Latem, Belgium) was used for pattern comparison. PFGE patterns were considered clonally related if they had a similarity coefficient >80%, optimisation 0.5% and tolerance 2.5% (the Dice similarity index and the unweighted pair group method with the arithmetic mean).

Antimicrobial resistance analysis was performed by the disc diffusion test according to the Clinical and Laboratory Standards Institute (2009). Fourteen antimicrobials were tested: ampicillin (10 μg), amoxicillin/clavulanic acid (20/10 μg), cefalothin (30 μg), cefoxitin (30 μg), cefpodoxim (10 μg), ceftazidime (30 μg), cefuroxime (30 μg), ciprofloxacin (5 μg), gentamicin (10 μg), kanamycin (30 μg), nalidixic acid (30 μg), streptomycin (10 μg), tetracycline (30 μg) and trimethoprim/sulfamethoxazole (1.25/23.75 μg). The reference strain *Escherichia coli* ATCC 25922 was used as the quality control.

Results

About 60% (75 out of 128) of the human *Y. enterocolitica* strains isolated from clinical samples belonged to biotypes

Table 1 *Y. enterocolitica* strains by gender and age collected during 2001 and 2010 in Switzerland from human clinical samples

Number of strains	Year	Gender			Age (years)					
		Female patients	Male patients	NK	<6	6–20	21–40	41–60	>60	NK
5	2001–2002	2	2	1	0	1	1	0	2	1
14	2003	7	7	0	1	0	3	8	2	0
12	2004	6	6	0	1	2	3	2	4	0
19	2005	5	14	0	0	2	7	4	6	0
21	2006	10	10	1	2	2	7	5	5	0
14	2007	9	5	0	0	4	2	4	4	0
11	2008	7	4	0	0	0	6	3	2	0
12	2009	6	5	1	0	3	6	2	0	1
20	2010	10	10	0	2	1	10	3	3	0
128	2001–2010	62	63	3	6	15	45	32	28	2

NK = not known

Table 2 *Y. enterocolitica* strains of different bioserotypes according to gender and age

Bioserotype	Number of strains (%)		Gender			Age					
			Female	Male	NK	<6	6–20	21–40	41–60	>60	NK
1A	51	(40)	29	21	1	1	7	15	14	13	1
2/O:5,27	4	(3)	2	2	0	1	0	1	1	1	0
2/O:9	22	(17)	13	9	0	1	2	7	4	8	0
3/O:3	2	(2)	0	2	0	0	1	1	0	0	0
4/O:3	47	(37)	17	28	2	3	5	21	11	6	1
NT	2	(2)	1	1	0	0	0	1	1	0	0

NK = not known; NT = not typeable

2, 3 or 4 which are considered to be pathogenic to humans (Table 2). However, a high number (51 out of 128, 40%) of *Y. enterocolitica* strains belonged to biotype 1A, which is regarded as non-pathogenic. The dominant pathogenic bioserotype was 4/O:3 (37%) followed by 2/O:9 (17%). Only 4 strains belonged to bioserotype 2/O:5,27 and 2 to bioserotype 3/O:3. Two strains did not belong to any of the known biotypes.

The *ail* gene was studied by PCR and it was detected in all 75 strains belonging to pathogenic bioserotypes 2/O:5,27, 2/O:9, 3/O:3 and 4/O:3. Surprisingly, *ail* was also detected in one strain belonging to non-pathogenic biotype 1A. This strain was isolated in 2007 from the faeces of a 62-year-old woman. Both strains of unknown biotype were *ail* negative. They were isolated from the faeces of a 40-year-old woman and a 50-year-old man in 2005. The two strains, which were not of any known biotype, were *ail* negative and pyrazinamidase positive, and thus were regarded as non-pathogenic *Y. enterocolitica*-like strains.

More *Y. enterocolitica* strains of biotype 1A and bioserotype 2/O:9 were from female than from male patients (Table 2). Strains belonging to bioserotype 4/O:3 were more frequently from males than from female patients. *Y. enterocolitica* of bioserotype 4/O:3 was isolated more often from patients between 0 and 40 years of age (29) than from patients over 40 (17; Table 2). Biotype 1A strains were the most common type in patients over 40 and they were frequently (18 out of 27, 67%) isolated from female patients.

Eight *Y. enterocolitica* strains were isolated from extra-intestinal sites: blood (4), liver (2), gall bladder (1), ulcer (1) and abscess (1). Strains of bioserotype 4/O:3 were isolated twice from blood and once from liver and ulcer. The 2 strains of bioserotype 2/O:9 were isolated from blood. Surprisingly, 2 strains belonging to biotype 1A were from extra-intestinal sites: the gall bladder and an abscess.

All 128 *Y. enterocolitica* strains were sensitive to ceftazidim (30 μg), ciprofloxacin (5 μg) and gentamycin (10 μg), and resistant to ampicillin (10 μg) and cefalothin

Table 3 Number of *Y. enterocolitica* strains showing resistance to antimicrobial agents

Antimicrobial agent	Bioserotype (number of strains)											
	1A (51)		2/O:5,27 (4)		2/O:9 (22)		3/O:3 (2)		4/O:3 (47)		NT (2)	
	I	R	I	R	I	R	I	R	I	R	I	R
Ampicillin	0	51	0	4	0	22	0	2	0	47	0	2
Amoxicillin/clavulanic acid	4	47	1	3	3	18	0	2	7	0	0	2
Cefalothin	0	51	0	4	0	22	0	2	0	47	0	2
Cefoxitin	22	23	0	4	3	18	0	2	0	0	1	1
Cefpodoxim	16	4	1	1	4	2	2	0	1	0	0	0
Cefuroxime	7	0	0	0	13	0	2	0	5	0	0	0
Kanamycin	0	3	0	0	0	0	0	0	0	0	0	0
Nalidixic acid	0	1	0	0	0	0	0	0	0	2	0	0
Streptomycin	3	0	0	0	0	0	1	0	5	7	0	0
Tetracycline	0	0	0	0	0	0	0	0	1	0	0	0
Trimethoprim/sulfa	0	0	0	0	0	0	0	0	2	1	0	0

NT = not typeable;
I = intermediate; R = resistant

(30 μg). Several strains were resistant to amoxicillin/clavulanic acid (20/10 μg) and cefoxitin (30 μg; Table 3). Interestingly, most strains belonging to bioserotypes 2/O:5,27 (3–4/4), 2/O:9 (18/22) and 3/O:3 (2/2) were resistant to amoxicillin/clavulanic acid and cefoxitin, but all 47 strains belonging to bioserotype 4/O:3 were sensitive to these agents. Sporadic resistance occurred to cefpodoxim (10 μg), kanamycin (30 μg), nalidixic acid (30 μg), streptomycin (10 μg) and trimethoprim/sulfamethoxazole (1.25/23.75). Strains belonging to bioserotypes 2/O:5,27 and 2/O:9 showed resistance cefpodoxim and strains of bioserotype 4/O:3 to streptomycin, nalidixic acid and trimethoprim/sulfamethoxazole (Table 3). Only 1 multi-drug resistant strain was detected. This strain was belonging to bioserotype 4/O:3 and it was isolated in year 2006 from the faeces of a 27-year old woman. It showed resistance to nalidixic acid, streptomycin and trimethoprim/sulfamethoxazole.

All 128 *Y. enterocolitica* strains were characterised by PFGE using the *XbaI* restriction enzyme. Strains belonging to bioserotypes 2/O:5,27 (2), 2/O:9 (22), 3/O:3 (2) and 4/O:3 (47) showed very limited genetic diversity; however,

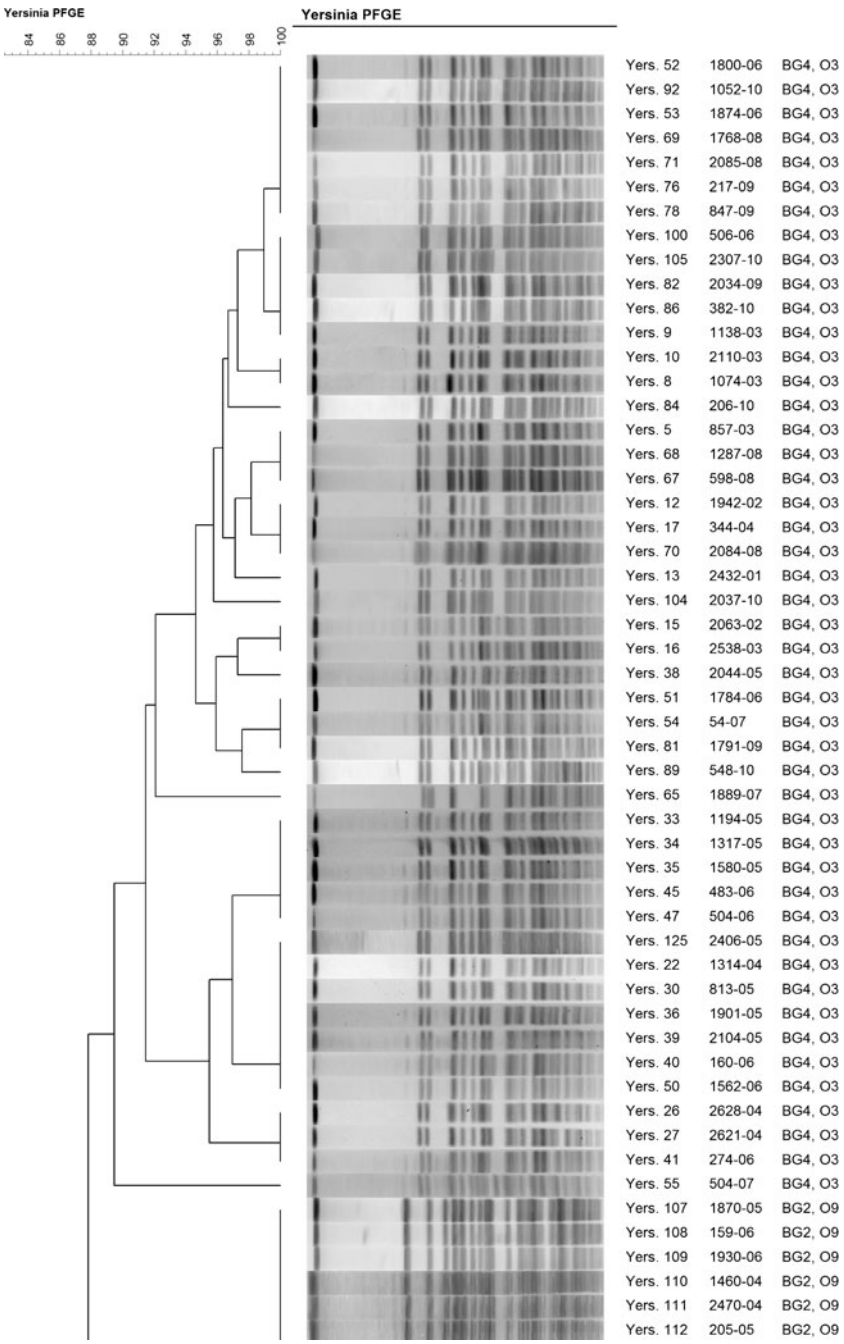
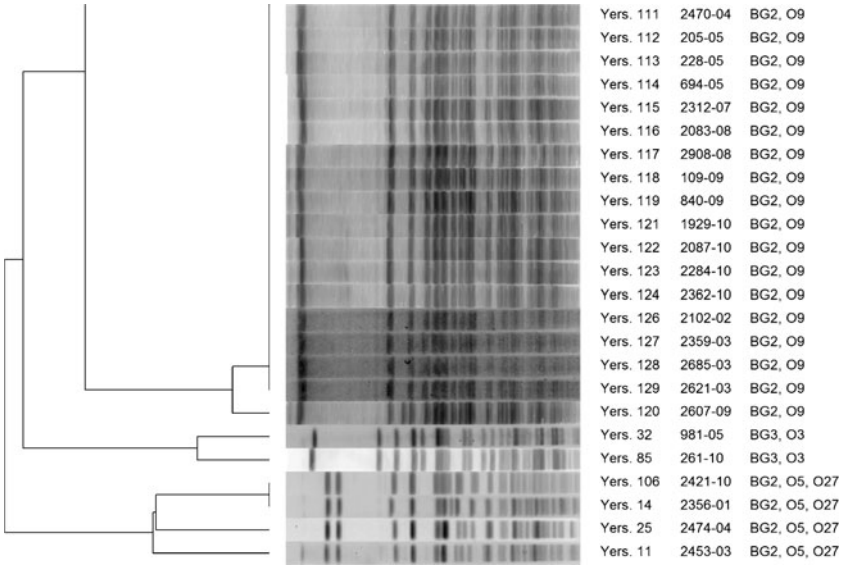


Fig. 1 Dendrogram of *Y. enterocolitica* strains belonging to biotypes 2, 3 and 4

Fig. 1 (continued)



each bioserotype differed clearly from all the others (Fig. 1). The 51 strains belonging to biotype 1A were very heterogeneous (Fig. 2). The *ail*-positive biotype 1A strain was grouped among the other biotype 1A strains (Fig. 2) and differed clearly from strains belonging to bioserotypes 2/O:5,27, 2/O:9, 3/O:3 and 4/O:3.

Discussion

Most of the human *Y. enterocolitica* strains belonged to the bioserotypes associated with human disease (75 out of 128). All these strains belonging to bioserotypes 2/O:5,27, 2/O:9, 3/O:3 and 4/O:3 were *ail* positive. The *ail* gene codes the Ail protein, which is involved in the attachment and invasion of the host cells and in the serum resistance of pathogenic *Y. enterocolitica* strains [8]. Bioserotype 4/O:3 was the most frequently identified pathogenic type (47 out of 75, 63%); however, the prevalence of bioserotype 2/O:9 (22 out of 75, 30%) was surprisingly high. Only 4 strains (5%) belonged to bioserotype 2/O:5,27 and 2 (3%) to bioserotype 3/O:3. In the last annual report of the European Centre for Disease Prevention and Control (ECDC), 8 European countries provided data on serotype; the two most common serotypes were O:3 (91%) and O:9 (7%) [2]. In Germany, of all the notified human cases with information on serotype, 89% were attributed to serotype O:3, and only 6% to serotype O:9 and 0.8% to serotype O:5,27 [1].

Only 6 (5%) patients reported having travelled abroad before infection, which indicates that the infections are domestically acquired. The majority (> 90%) of yersiniosis cases in Europe have also been reported to be domestically acquired [1, 2]. In Switzerland, pigs at slaughter have been shown to carry *ail*-positive *Y. enterocolitica* bioserotype 4/O:3 frequently in the tonsils [4], which shows that domestic pigs can be an important source of human bioserotype 4/O:3 infection in Switzerland. Pigs have been shown to be an important reservoir and pork an important source of human *Y. enterocolitica* 4/O:3 infection in Germany and Finland [9]. Bioserotypes 2/O:5,27 and 2/O:9 have been sporadically isolated from Swiss pigs and could thus also be the source of human infections. However, the prevalence of bioserotype 2/O:9 was high in human infections, which indicates that there may be infection sources other than pigs. Two human strains belonged to bioserotype 3/O:3, which can indicate an Asiatic origin because this bioserotype is mainly reported in Asia [10]. However, bioserotype 3/O:3 has also been sporadically isolated from chinchillas in Europe [11].

Some of the *Y. enterocolitica* strains belonging to bioserotypes 2/O:9 and 4/O:3 (6 out of 69) were isolated from extra-intestinal sites. Extra-intestinal infections are rare and usually described in humans who are immune-compromised or in those with iron overload [12]. *Y. enterocolitica* 4/O:3 was isolated once from liver and skin lesions. Two strains of type 2/O:9 (9%) and 4/O:3 (4%) were isolated from blood, showing that these bioserotypes are not uncommon causes of bacteraemia in humans. *Y. enterocolitica* was one of the first recognised causes of post-transfusion sepsis [13]. Serotypes O:3 and O:9 are the most common types attributed to post-transfusion septic shock. Because *Yersinia* has the property to grow at 4°C, the low number of *Y. enterocolitica* strains collected from asymptomatic donors can lead to a high bacterial load if the blood products are stored for some weeks.

Y. enterocolitica strains belonging to biotype 1A are considered non-pathogenic to humans because they lack the major virulence determinants [14]. However, the number of strains belonging to biotype 1A was high (40%) among

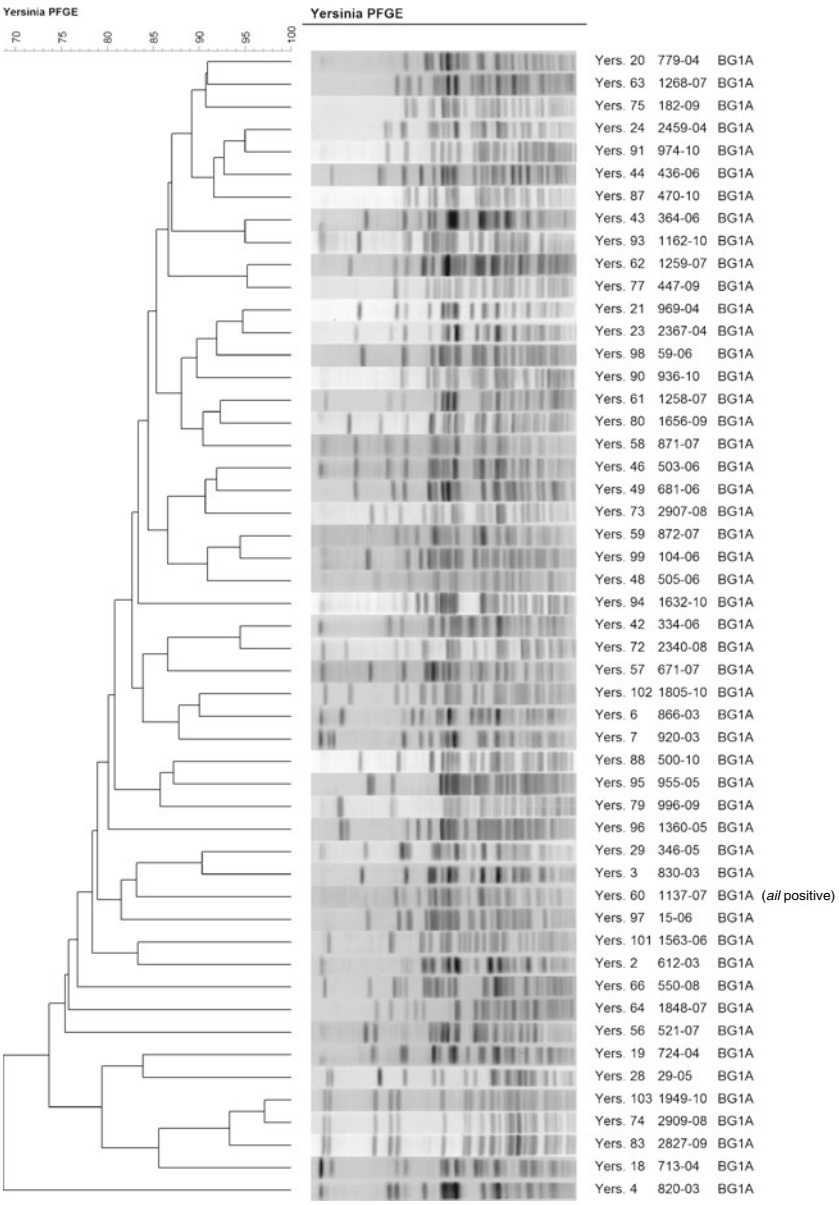


Fig. 2 Dendrogram of *Y. enterocolitica* strains belonging to biotype 1A

human patients in Switzerland. In Finland, an even higher prevalence (64%) of strains belonging to this biotype was recently reported [15]. One reason might be that in Finland, but not in Switzerland, cold enrichment, which increases the number of biotype 1A strains, is frequently used for human clinical samples. *Y. enterocolitica* strains belonging to biotype 1A lack the *ail* gene, which is an important chromosomal virulence gene found only in strains belonging to biotypes 1B and 2–5. Surprisingly, 1 of 51 strains of biotype 1A (2%) was *ail*-positive. Recently, Sihvonen et al. reported 1 *ail*-positive strain among 299 human clinical *Y. enterocolitica* biotype 1A strains, which shows that the *ail* gene is not a common finding among clinical biotype 1A strains [16].

Y. enterocolitica biotype 1A strains were mostly (49 out of 51) isolated from faeces. Surprisingly, *Y. enterocolitica* biotype 1A strains were also isolated from the gall bladder and from skin lesions. The clinical disease with which *Y. enterocolitica* biotype 1A has been reported to be associated is enteritis [17]. Biotype 1A strains have previously been isolated from blood, but not from other extra-intestinal sites. However, the pathogenic potential and true public health significance of *Y. enterocolitica* biotype 1A strains are still unclear [17].

The highest notification rate has been in children under 5 years of age in Europe followed by the age group 5–14 years [2]. However, *Y. enterocolitica* was seldom isolated from young children under 6 years of age (6 out of 128) and from patients between 6 and 20 (15 out of 128) in Switzerland. One reason might be the high number of biotype 1A strains that were commonly found in patients

over 20 years of age. In a recent study, the symptoms of the patients with *Y. enterocolitica* biotype 1A differed from yersiniosis caused by the pathogenic biotypes [5]. Patients infected with pathogenic biotype strains were younger (mean age: 32 years and 50 years respectively), had fever (67% and 35% respectively) and reactive arthritis more often (10% and 3% respectively) than those with biotype 1A strains, which suggests the lacking virulence of biotype 1A strains. However, more research is needed to study the potential pathogenicity of biotype 1A strains.

Bioserotype 4/O:3 strains were more often isolated from male (28 out of 47) than from female patients (17 out of 47). In Germany, where strains of biotype 4/O:3 strain dominate, the infections occurred more frequently in boys and men than in girls and women [1]; however, there was no explanation for this phenomenon. Surprisingly, biotype 1A strains were more often found in female patients, especially in women over 40, than in male patients. One explanation for the higher prevalence of biotype 1A strains among women over 40 might be that they visit the doctor more frequently than men.

Human *Y. enterocolitica* strains showed susceptibility to most antimicrobials other than β-lactams. All strains were susceptible to ceftazidime, ciprofloxacin and gentamicin and only sporadically resistant to cefpodoxim, kanamycin, nalidixic acid, streptomycin and trimethoprim/sulfamethoxazole. Interestingly, most of the biotype 2 and 3 strains were resistant to amoxicillin/clavulanic acid and cefoxitin when all biotype 4/O:3 strains were sensitive, indicating an association between susceptibility to amoxicillin/clavulanic acid and cefoxitin and biotype. Only one strain, which belonged to bioserotype 4/O:3, showed resistance to multiple microbial agents: streptomycin, nalidixic acid and trimethoprim/sulfamethoxazole. Multi-resistance has been shown to be rare among *Y. enterocolitica* strains in Switzerland and Germany [18, 19]. In a recent study from Finland, multi-resistance was significantly associated with travelling abroad [6]. Surprisingly, 3 *Y. enterocolitica* strains (1 biotype 1A and 2 biotype 4/O:3 strains) were resistant to nalidixic acid, which has not been reported before in Switzerland.. It has been shown that nalidixic acid resistance correlates with decreased susceptibility to ciprofloxacin in MIC determination [6], which can be problematic in the treatment of complicated yersiniosis cases.

All strains were characterised with PFGE using *Xba*I. This restriction enzyme was used in the PulseNet protocol and in an earlier Swiss study [19]. PFGE with *Xba*I distinguished the different biotypes from each other and can thus help to identify *ail*-positive *Y. enterocolitica* strains of different biotypes. Strains belonging to biotypes 2, 3 and 4, which all carried the *ail* gene, exhibited high homogeneity. However, strains belonging to serotypes O:5,27 and O:9 of biotype 2 could also easily be differentiated from each other. Strains belonging to biotype 1A, including the one *ail*-positive strain, appeared to be highly heterogeneous. High genetic diversity among biotype 1A strains has also been demonstrated by amplified fragment length polymorphism (AFLP) typing [20]. High genetic diversity is a common feature among non-pathogenic, environmental bacteria when most of the pathogenic bacteria are usually genetically monomorphic [21].

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