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The Epidemiology and Zoonotic Transmission of Thermophilic *Campylobacter lari*

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Review Article

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ABSTRACT

Thermophilic campylobacters, including *Campylobacter lari*, are the most common cause of acute bacterial gastroenteritis in the developed world. Although *C. jejuni* and *C. coli* account for the majority of these cases, *C. lari* has been described from about 30 cases in several countries over the last 20 years and this species has been shown to be a severe and potential pathogenic agent for humans, manifesting as gastroenteritis, diarrhea, septicemia and bacteremia. *Campylobacter lari* is most prevalently isolated from seagulls in the natural environment, followed by water and shellfish in several European countries and in one Asian country, Japan. The prevalence of poultry with *C. lari* has been demonstrated in Japan, the USA, England, Poland, Tanzania, Peru, Denmark, Kenya and Northern Ireland, indicating that contamination of poultry with this species is common and widespread. Moreover, *C. lari* has also been distributed in dogs, cats, pigs, cattle and sheep in several countries. Thus, the natural environment including wild birds and some domestic animals, mainly poultry, may be considered as important reservoirs of *C. lari*.
This review aims at describing (i) the historical evolution of *C. lari*, (ii) its reservoirs for human infection, including the natural environment and zoonotic hosts, (iii) cases of human infection reported and (iv) its pathogenesis.

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1. INTRODUCTION

Campylobacter lari was first isolated from mammalian and avian species, especially seagulls of the genus Larus (Skirrow & Benjamin, 1980; Benjamin et al., 1983). Although *C. lari* is seen infrequently as a cause of clinical infection in humans (Braneau et al., 1998), detailed cases of humans clinical illness associated with *C. lari* failed to emerge for several years, although several cases of human illness associated with *C. lari* have now been reported in recent years (Godreuil et al., 2000; Martinot et al., 2001; Prasad et al., 2001; Warno et al., 2002; Krause et al., 2002). Five recent cases strongly demonstrate that C. lari is a potential human pathogen causing enteritis and diarrhea in immunocompetent patients and bacteremia in immunocompromised patients. Moreover, in veterinary medicine, there have been reports of the isolation of this organism from domestic animals including chickens (Tresierra-Ayala et al., 1994; Stanley et al., 1998; Jones et al., 1999; Raji et al., 2000; Wedderkopp et al., 2000) and pigs (Moore and Maden, 1998, 2003). Thus, reports of contamination of humans and domestic animals, with *C. lari* have gradually increased over several years. However, an underestimation of risk factors of *C. lari* with human illness is likely. Therefore, the aim of the present review is to examine the overall history of detection and isolation of *C. lari*, as well as to identify the reservoirs of *C. lari* and finally to discuss the possibility of significant risk factor(s) of *C. lari* for human infections.

2. FIRST ISOLATION OF *C. lari* BY SKIRROW AND BENJAMIN

Skirrow and Benjamin first described 42 new thermophilic Campylobacter strains which were nalidixic acid (NAL) resistant and salt tolerant and referred to these as "nalidixic acid-resistant thermophilic Campylobacter (NARTC)" in 1980 (Skirrow & Benjamin, 1980). Among the 42 strains, the first isolation was made from the faeces of a symptomless six-year-old boy in 1976, but most isolates (n=26) were obtained from wild birds, particularly seagulls. Of the other 15 isolates, ten were isolated from domestic animals (dogs, cats and poultry). Benjamin et al. first employed the name Campylobacter laridis (Benjamin et al., 1983), and the name was later revised to *Campylobacter lari* (Von Graevenitz, 1990).

3. ISOLATION OF *C. lari* FROM THE NATURAL ENVIRONMENT

Shortly after these two descriptions mentioned above, faecal samples from 942 herring gulls caught in Scotland from 1982-1988, were examined and showed that 64% of the birds were positive for Campylobacter spp., of which 54% were *C. lari* (Whelan et al., 1988), suggesting a high prevalence of this Campylobacter species in herring gulls. Mawer isolated eight strains of *C. lari* from ponds, lakes, land drains and river sites in England in 1983 (Mawer, 1988). In addition, Fricker and Park isolated a strain of *C. lari* from sewage and then 16 strains from river water, over a two-year period in England from 1984 (Fricker and Park, 1989).

In Japan, Kaneuchi et al. examined a total of 170 seagulls faeces collected in 1985, which were successfully identified and isolated 34 strains of *C. lari* by DNA-DNA hybridization (Kaneuchi et al., 1987, 1988). In addition, Murayama et al. isolated a total of 30 isolates of

C. lari from fecal droppings of crows in Japan during the period from 1986 to 1987 (Murayama et al., 1990).

In addition, Bolton et al. isolated the first 10 strains of urease-positive thermophilic Campylobacter (UPTC) from the natural environment, namely river water, seawater, mussels and cockles in England in 1985 (Bolton et al., 1985). This was the first demonstration of the occurrence of UPTC strains. Then, Bolton et al. also isolated 10 strains of *C. lari* and some strains of a previously unrecognized NAL-sensitive group of campylobacters (NASC) from river water in England (Bolton et al., 1987). Following this, Owen et al. suggested that UPTC and NASC strains belonged within *C. lari*, possibly as biovars based on the numerical analysis of protein gel electrophoresis (Owen et al., 1988).

In Germany, strains of *C. lari* were obtained from sewage in Kiel (Höller, 2000) and five strains of *C. lari* were isolated from silver gulls and 13 from three-toed gulls (Glunder & Petermann, 1989). Wilson and Moore isolated a total of 42% of Campylobacter spp. isolates from 380 shellfish of bivalve molluscs in Northern Ireland in 1994, and the percentages of *C. lari* among these isolates were: urease-negative *C. lari*, 24%; UPTC, 57% (n=91; Wilson and Moore, 1996). Because of the great percenage of UPTC, they pointed out that urease test should be included in the characterization of campylobacters from marine environments and fecal specimens.

During 1993, Endtz et al. examined the presence of *Campylobacter* spp. of 59 batches of mussels and 41 batches of oysters harvested from marine waters in the Netherlands and detected *Campylobacter* spp. from 41 out of batches of mussels (69%) and from 11 out of oysters (27%) (Endtz et al., 1997). When they characterized 39 *Campylobacter* spp. by additional phenotypic tests, numerical analysis of electrophoretic protein patterns and genotyping by random amplification of polymorphic DNA, 37 strains were identified as *C. lari* and 14 of *C. lari* were UPTC. In Japan, the first finding of two UPTC strains, CF89-12 and CF89-14, in the water from two different rivers in Okayama was demonstrated (Matsuda et al., 1996). The pulsed-field gel electrophoresis analysis suggested both genomes of approximately 1,862 kb in size. In fresh fecal samples taken from wild birds in England in 1996, *C. jejuni, C. coli*, *C. lari* and a large proportion of UPTC were identified (Fitzgerald et al., 1998). This was the first report of UPTC isolated from wild birds. In Northern Ireland, in 205 fresh fecal specimens collected from members of the gull family from three costal locations, Campylobacter spp. was detected to be positive in 28 (Kaneko et al., 1999; Moore et al., 2002a). Of these, 21 belonged to the UPTC taxon, followed by five *C. lari* and two urease-negative *C. jejuni*. Consequently, it was strongly suggested that seagulls are the sole warm-blooded animal host of this UPTC taxon in Northern Ireland.

Popowski et al. examined the presence of thermotolerant *Campylobacter* in rivers and lakes of Warsaw region in Poland, and indicated about 70% of water samples contaminated with campylobacter (Popowski et al., 1997). The species distribution was as follows: *C. jejuni*-65%, *C. Coli*-22%, *C. lari*-13% and the highest contamination with campylobacter was concluded to be connected mainly with the presence of municipal sewage and to a lesser extent, with the presence of fecal droppings from wild animals. When Obiri-Danso and Jones measured distribution of thermophilic *Campylobacter* in two freshwater bathing sites on the River Lune in England, between 1996 and 1997, Campylobacter (236 isolates) were mainly *C. jejuni,* followed by *C. coli*, UPTC (6-10%) and *C. lari* (4-9%) (Obiri-Danso and Jones, 1999). Moreover, of the 82 *Campylobacter* isolates obtained from mallard feces, 90% were C. jejuni, 7% C. Coli and 3% UPTC. In Japan, Misawa et al. isolated a strain of *C. lari* from a fecal specimen of a Chillian Flamingo at Zoo (Misawa et al., 2000). When Rosef et al. examined the occurrence of *C. jejuni*, *C. coli* and *C. lari* in Bo River water in Norway, of the

75 strains, *C. Coli* was the dominant species followed by *C. jejuni* and *C. lari* (14.7%) (Rosef et al., 2001).

In Japan, two UPTC strains were found from crows around Yokohama in 1998 (Matsuda et al., 2002). Most recently, Waldenström et al. recovered 72 UPTC isolates from Redshanks on grazed coastal meadows in southern Sweden (Waldenström et al., 2003).

Thus, as shown in Table 1, *C. lari* has been commonly isolated from seagulls among the natural environment followed by water and shellfish. Moreover, it is very characteristic and interesting that a total of 32 strains of *C. lari* were isolated from crows in Japan.

Table 1. Summary of the isolation of urease-negative thermophilic *Campylobacter* from the natural environment

Country	Year	Source	References
England	NK	Seagulls, bird, water	Skirrow and Benjamin,1980 Benjamin et al., 1983
Scotland	1982-1985	Faeces of herring gulls	Whelan et al., 1988
England	NK	Ponds, lakes, land drains, river sites	Mawer, 1988
England	1984-1986	Sewage, river water	Fricker and Park, 1989
Japan	Apr-June 1985	Faeces of seagulls	Kaneuchi et al., 1987, 1988
England	NK (12.5 months)	River water	Bolton et al., 1987
Japan	May 1986-Apr 1987	Fecal droppings of crows from a seashore and a cemetery	Murayama et al., 1990
Germany	NK	Herring gulls, Kittiwakes	Glunder and Petermann, 1989
Germany	July1985-Aug 1986	Sewage	Holler et al., 1988
Northern Ireland	Jan-Dec 1994	Shellfish seawater	Wilson and Moore, 1996
The Netherlands	Sep 1993-Feb 1994	Shellfish	Endtz et al., 1997
Northern Ireland	July-Aug 1996	Feces of seagulls	Moore et al., 2002a
Poland	NK	Rivers, lakes	Popowski et al., 1997
Engalnd	1996-1997	Freshwater bathing sites	Obiri-Danso and Jones, 1999
Norway	NK	River	Rosef et al., 2001

NK, not known

Consequently, until now, urease-negative *C. lari* strains have been reported to be detected and isolated from the natural environment in several European countries and in one Asian country, Japan. Moreover, a summary of the isolation of UPTC is shown in Table 2.

Table 2. Isolation of urease-positive thermophilic *Campylobacter* (UPTC)

Country	Year	Source	No. of isolates obtained	References
England	1985	River water, seawater mussels, cockles	10	Bolton et al., 1985 Owen et al., 1988
France	1986-1989	Humans	4	Megraud et al., 1988 Bezian et al., 1990
Northern Ireland	Jan-Dec 1994	Seawater, shellfish	>90	Wilson and Moore, 1996
The Netherlands	1993-1994	Shellfish (mussels, oysters)	14	Endtz et al., 1997
Japan	NK	River water	2	Matsuda et al., 1996
England	1996	Fresh feces from wild birds	A large proporation	Fitzgerald et al., 1998
Northern Ireland	1996	Fresh feces from seagulls	21	Kaneko et al., 1999; Moore et al., 2002a
England	1996-1997	Two freshwater bathing sites	6-10% of 236 strains	Obiri-Danso and Jones, 1999
England	1996	Mallard fecal samples	3% of 82 strains	Obiri-Danso and Jones, 1999
Japan	1998	Intestinal contents of crows	2	Matsuda et al., 2002
Sweden	NK	Redshanks	72	Waldenstrom et al., 2003

NK, not known

4. ISOLATION OF *C. lari* FROM DOMESTIC ANIMALS

Shortly after the first demonstration of the occurrence of *C. lari* in the natural environment (Skirrow and Benjamin, 1980), a *C. lari* strain from the intestine of a horse (country, Sweden; isolation year, 1981) was described in the literature (Duim et al., 2001). Yoshida et al. firstly isolated *C. lari* from nine hens on 10 farms in Japan between 1983 and 1984 (Yoshida et al., 1987). This was the first isolation of *C. lari* from chicken, suggesting its occurrence in domestic animals in early 1980s. In Victoria, Australia, Coloe et al. isolated two *C. lari* strains from intestinal tracts of food animals and identified strains using gas-liquid chromatographic analysis of cellular fatty acids (Coloe et al., 1986). When Totten et al. examined strains of thermophilic *Campylobacter* isolated from humans with diarrhea and from poultry, as part of a large epidemiological study in King County, Washington, one strain of *C. lari* was detected from poultry (Totten et al., 1987). In that study, they used a rapid DNA hybridization test to discriminate thermophilic Campylobacter species without extracting the genomic DNA.

In Japan, two strains of *C. lari* were isolated from the feces of healthy dogs (Kaneuchi et al., 1988). In addition, eight strains of *C. lari* were isolated from colonal contents of slaughtered pigs. Fricker and Park examined the distribution of thermophilic *Campylobacter* in food samples from the Reading area in England for two years from 1984, where they described two C. lari strains from poultry and one from an offal source (Fricker and Park, 1989). When Kwiatek et al. examined the prevalence and distribution of *Campylobacter* spp. on 839 poultry (chickens, ducks, geese and turkeys), 105 pork and 114 beef in Poland, *C. lari* was detected in 10 chickens, 18 ducks, and 4 geese, thus demonstrating that poultry appear to be contaminated by *C. lari*, as well as *C. jejuni* in Poland (Kwiatek et al., 1990). Lindblom et al. isolated eight strains of *C. lari* from Swedish pigs (Lindblom et al., 1990). This is the second demonstration of *C. lari* from pigs following Kaneuchi's report in Japan. Then, in 1990s, *C. lari* strains were demonstrated from cattle in Japan (Giacoboni et al., 1993), from droppings of poultry in eastern zone of Tanzania (Kazwala et al., 1993), from chickens in Iquitos, Peru (Tresierra-Ayala et al., 1994), from broilers and cattle in Denmark (Aarestrup et al., 1997), and from chickens in Lagos, Nigeria (Smith et al., 1997). In relation to Peru, 21 strains of *C. lari* were isolated from cloacal swabs of 200 chickens, and chicken was demonstrated as potential source of contamination of *C. lari* in Iquitos, Peru (Tresierra-Ayala et al., 1994).

When a total of 88 randomly selected broiler flocks were examined in Danish broiler production in 1995, 52% of the flocks were found to be *Campylobacter* spp.-positive before slaughter (Hald et al., 2000). The species distribution was 87% of *C. jejuni*, 8% of *C. coli* and 5% of *C. lari*.

Stanley et al. measured distribution of *Campylobacter* species of strains (n=1250) isolated from the small intestinal contents of lambs at slaughter from markets and farms all over the north-west of England, North Wales and southern Scotland on a monthly basis over a 2-year period, *Campylobacter* could be isolated from 91.7% (n=360) of samples, where 0.2% was *C. lari* (Stanley et al., 1998). Jones et al. measured the rates at which sheep on different types of pasture shed campylobacters in their feces within five miles of Lancaster over 12 months from May 1996 (Jones et al., 1999). Consequently, a total of 34% of sheep feces was thermophilic *Campylobacter* spp.- positive and *C. jejuni* was the main species, followed by *C. coli* and *C. lari* (2%).

In Africa, Osano and Arimi isolated *C. lari* (2%) from raw chickens in Nairobi, Kenya (Osano and Arimi, 1999) and Raji et al. isolated three isolates of *C. lari* from sheep in Kaduna State, Nigeria, (Raji et al., 2000).

Wedderkopp et al. performed national surveillance of Campylobacter in 57,000 broilers of 4286 broiler flocks at slaughter in Denmark in 1998, and overall, a flock prevalence of 46% was recorded (Wedderkopp et al., 2000). The species distribution was demonstrated to be *C. jejuni* 86%, *C. Coli* 11% and *C. lari* 1%. When Moore et al. examined the prevalence of thermophilic Campylobacter spp. in 107 raw chickens (63 fresh and 44 frozen) in Northern Ireland, 94% of the fresh birds and 77% of the frozen examined were contaminated (Moore et al., 2002b). *C. jejuni, C. Coli* and *C. lari* accounted for 69, 30, and 1% of the contaminating organisms, respectively. Moreover, Moore and Madden examined the occurrence of thermophilic Campylobacter spp. in pork liver (n= 400) from bacon pigs (37 herds) in Northern Ireland and revealed that about 6% of livers were infected with Campylobacter spp., consisting of *C. coli* (67%), *C. jejuni* (30%) and *C. lari* (3%) (Moore and Madden, 1998, 2003).

In the midwestern USA, Logue et al. examined the incidence of *Campylobacter* spp. on turkeys presented for processing at two processing plants over a period of one year for the three sampling points tested, i.e., prechill, postchill and chill water, and several percentages of C. lari were recovered from postshill swabs isolated from a plant (Logue et al., 2003).

The prevalence of poultry with *C. lari* has been demonstrated in Japan, the USA, England, Poland, Tanzania, Peru, Denmark, Kenya, and Northern Ireland, indicating that the contamination of poultry with *C. lari* is common (Table 3). Moreover, the distributions of *C. lari* have also been demonstrated in dogs, cats, pigs, cattle, sheep, turkeys and a horse in several countries. Thus, in conclusion, the natural environment including wild birds and some domestic animals, mainly poultry, have been shown to be important reservoirs of *C. lari*. Therefore, untreated drinking water, shellfish and domestic animals, mainly poultry, could be important risk-factors of human illness associated with *C. lari*.

Table 3. Examples of the isolation of urease-negative *Campyloabcter* from domestic animals

Country	Year	Source	References
England	NK	Dogs, cats, poultry	Skirrow and Benjamin, 1980
Japan, Tokyo and Kanagawa	June 1983-June 1984	Hens	Yoshida et al., 1987
Australia, Victoria	NK	Food animals	Coloe et al., 1986
the USA, Washington State	NK	Poultry	Totten et al., 1987
Japan	For two years from 1984	Dogs, pigs	Kaneuchi et al., 1988
England, Reading	NK	Poultry, offal	Fricker and Park, 1989
Poland	NK	Chickens, ducks, geese	Kwiatek et al., 1990
Sweden	NK	Pigs	Lindblom et al., 1990
Japan	NK	Adult cattle	Giacoboni et al., 1993
Tanzania, eastern zone	NK	Poultry dropping	Kazwala et al., 1993
Peru, Iquitos	NK	Cloacal swabs of chickens	Tresierra-Ayala et al., 1994
Denmark	NK	Broilers, cattle	Aarestrup et al., 1997
Nigeria, Lagos	NK	Chicken	Smith et al., 1997
Denmark	May-July 1995	Broiler	Hald et al., 2000
UK	For over a 2-year period from 1994	Intestine content of lambs	Stanley et al., 1998
England, Lancaster	For over 12 months from 1996	Feces of sheep	Jones et al., 1999

Table 3 continued…..

Kenya, Nairobi	NK	Chickens	Osano and Arimi, 1999
Nigeria, Kaduna State	NK	Sheep	Raji et al., 2000
Denmark	1998	Broilers	Wedderkopp et al., 2000
Northern Ireland	NK	Chickens	Moore et al., 2002b
Northern Ireland	NK	Pork livers from bacon pigs	Moore et al., 1998, 2003
The midwestern USA	NK (over a period of 1 year)	Turkey	Logue et al., 2003

NK, not known

5. CLINICAL ISOLATION OF *C. lari* FROM HUMANS

Although many strains of *C. lari* have been detected from the natural environment and domestic animals in Europe as described above, it was in North America where several clinical strains were first detected and isolated from humans. Firstly, Nachamkin et al., at the University of Pennsylvania, isolated a *C. lari* organism from the blood of a 71-year-old man who was immunosuppressed with multiple myeloma, hyperviscosity syndrome, and renal failure (Nachamkin et al., 1984). This was the first recorded case of bacteremia due to *C. lari* in humans. Following this, Tauxe et al. reported six clinical isolates of *C. lari* organism obtained from a 71-year-old man, a 39-year-old woman, a 22-year-old woman, a 7-year-old girl, a 3-year-old boy and a 8-month girl, where enteritis was reported in four, severe crampy abdominal pain in one, and terminal bacteremia in an immunocompromised host in another (Tauxe et al., 1985). In Canada, a previously healthy 32-year-old male, with a self-limiting diarrheal illness, whose stool cultures yielded *C. lari* was described (Simor and Wilcox, 1987). Moreover, he developed a specific serum bactericidal antibody response to this strain. In Canada, moreover, a water-borne outbreak of *C. lari*-associated gastroenteritis occurred in March, 1985 (Broczyk et al., 1987). A power station's municipally treated drinking water supply was accidentally contaminated by a faulty plumbing connection with surface water from Lake Ontario. When stool specimens were collected after the onset of symptoms from 125 patients, *C. lari* was isolated from seven patients, among 162 symptomatic cases, mostly in construction workers.

Moreover, in Victoria, Australia, Coloe et al. isolated three *C. lari* strains among 23 from human stools of patients with gastroenteritis and identified strains by using gas-liquid chromatographic analysis of cellular fatty acids (Coloe et al., 1986). C. lari isolates contained 14:0, 3-OH 14:0, 16:1, 16:0 and 18:1 fatty acid, but not 19:0 cyclopropane fatty acid. In Europe, Bär et al. identified five strains of C. lari among 658 strains of thermopohilic Campylobacter species isolated from infected humans from the 10 cities in the southwest of Germany in 1985 and 1986 (Bär et al., 1989). Then, three strains of *C. lari* were isolated from a patient with diarrhea in France (Darbas et al., 1987), from a diarrheric AIDS patient with bacteremia in Italy (Dionisio et al., 1989, 1991), and from a patient associated with gastroenteritis in Sweden (Söderström et al., 1991). In Australia, two strains of *C. lari* were identified among diarrhoeal stools from 676 patients, mostly aboriginals aged less than 5 years between 1988 and 1989 (Albert et al., 1992). Moreover, the first clinical isolation of *C. lari* and identification of a reservoir in Chile was demonstrated (Fernandez et al., 1990). Gaunt and Piddock identified and isolated six strains of *C. lari* among 2209 clinical isolates of Campylobacter spp. collected at Plymouth Public Health Laboratory in 1991 (Gaunt and Piddock, 1996). Eyers et al. isolated the 13 strains of *C. lari* from diarrheic stool specimens in Brussels and identified 13 strains as *C. lari* by molecular discrimination using a 23S rDNA fragment (Eyers et al., 1993). When Skirrow et al. performed routine surveillance of gastrointestinal infections in England and Wales from 1981 to 1991, two campyloabcter bacteraemia were due to *C. lari* (Skirrow et al., 1993). In Rosario, Argentina, one strain of *C. lari* was isolated and identified among enteropathogenic organisms from paediatric patients with acute diarrheal disease from 1985 to 1993 (Notario et al., 1996). Evans and Riley, at the University of Utah, reported *C. lari* colitis in a 32-year-old woman, who was AIDS-positive, in July 1992 (Evans and Riley, 1992a). Since Evans and Riley described this *C. lari* strain as NAL resistance and hippurate hydrolysis, Nachamkin, who firstly found a clinical isolate of *C. lari* in 1984, pointed out their misidentification of NAL-resistant *C. jejuni* but not *C. lari* (Nachamkin, 1992). However, they soon appreciated this, and now noted that that original isolate of *C. lari* was indeed negative for hippurated hydrolysis (Evans and Riley, 1992b). In 1992, two strains of *C. lari* were reported from two patients with HIV infection in Palma and Sevilla, Spain (Reina et al., 1992; Vargas et al., 1992).

In 1995, several reports of *C. lari* clinical infection were made, namely in a neonate (25-day-old) with chronic diarrhea and bacteremia caused by *C. lari* in Taiwan (Chiu et al., 1995), a 17-year-old male with reactive arthritis as a complication of *C. lari* enteritis in the Netherlands (Goudswaard et al., 1995), and the three clinical isolates of *C. lari* in Malaysia (Tay et al., 1995). In the case of the Netherlands, an otherwise healthy young man surprisingly developed enteritis and reactive arthritis after having taken a swim in a salt-water lake. When Lin et al. isolated 162 strains of Campylobacter spp., 154 strains of which were from younger than five years, among 6,549 patients with diarrhea or gastroenteritis in central Taiwan from 1994 to 1996, they identified 16 strains of *C. lari* (Lin et al., 1998). In 1995, an 80-year-old debilitated male patient developed purulent pleurisy caused by a *C. lari* isolate in France (Bruneau et al., 1998).

Lawson et al. extracted DNA from 3,738 fecal samples from patients with sporadic cases of acute gastroenteritis, submitted by seven regional Public Health Laboratories in England and Wales over a 2-year period and performed a PCR-based study of the incidence of enteropathogenic Campylobacter infection in humans (Lawson et al., 1999). One case was attributed to *C. lari*. When Thwaites and Frost examined 5,802 isolates of thermophilic Campylobacter isolated from humans with diarrheal disease in North West England and Wales in 1997, 25 isolates were identified as *C. lari* (0.5%) (Thwaites and Frost, 1999).

In 1998, Morris et al. described the first case of a previously healthy 83-year-old woman with recurrent *C. lari* pacemaker infection and bacteremia (Morris et al., 1998). Her medical history included pacemaker implantation 4 years earlier and coronory artery bypass 6 years before implantation. In France in 1999, two cases of *C. lari* bacteremia of a 90-year-old man (Godreuil et al., 2000) and of a 10-year-old girl who underwent an occipital cavernoma exision occurred (Martinot et al., 2001). In the literature, Martinot et al. described that nine fecal specimens were positive for *C. lari* (3%) among 319 stool cultures positive for Campylobacter spp. at Strasbourg University Hospital from 1995 to 1999. During the same period, 16 blood cultures were positive for Campylobacter spp., one being *C. lari* (6%).

When Prasad et al. isolated 62 isolates of *Campylobacter* spp. from stool samples of patients with diarrhea from a tertiary care center in north India, over a 12-year period, two isolates of *C. lari* were identified (Prasad et al., 2001).

Then, in 2002, two cases of *C. lari* septicemia in two immunocompetent patients were reported. Firstly, in New Zeeland, Werno et al. described a fatal case of *C. lari* prosthetic joint infection and bacteremia in an 81-year-old male immunocompetent patient, for whom the right total hip prosthesis was inserted 4 years previously for osteoarthritis (Werno et al., 2002). In this case, the identification of the isolate was confirmed by a multiplex PCR targeting of the *Campylobacter* 1pxA gene. Secondly, in Austria, a severe and recurrent septicemia due to *C. lari* and *C. fetus* in an immunocompetent, 75-year-old, patient was reported (Krause et al., 2002). They employed PCR tests based on species-specific nucleotide sequences for the 16S rDNA, as well as on phenotypic characteristics for the identification of *C. lari* and *C. fetus*. These two reports in 2002 suggest that *C. lari* may cause severe disease, even in the immunocompetent host.

Until now only four clinical isolates of UPTC, characterized as a variant or biovar of *C. lari*, two from the feces of a 50-year-old man and a 60-year-old woman with diarrheal disease in 1986, one from an appendix of a 10-year-old boy with appendictis 1987, and one from the urine of a patient of 54-year-old man with urinary tract infection in 1989, have been identified (Mégraud et al., 1988; Bézian et al., 1990; Table 2). However, any association of UPTC with these disease still remains unclear.

Although so far, most cases of human illness associated with *C. lari* have been recognized infrequently, to date, clinical reports involving patients of the disease associated with this organism clearly demonstrated a total of *C. lari* isolates more than 110 in ten and several countries, since the first clinical report in human in 1984 (Table 4). The present article also demonstrated that *C. lari* is causative agents of human gastroenteritis, diarrhea, septicaemia, bacteremia and so on and may cause severe disease, even in an immunocompetent host, almost similar to *C. jejuni*, but likewise infrequently, compared to cases caused by *C. jejuni*.

6. EXAMPLES OF CLINICAL ISOLATES FROM HUMANS ANALYZED IN IDENTIFICATION AND DISCRIMINATION STUDIES AND DESCRIPTIONS OF THEIR SOURCES

Some clinical isolates from humans have appeared in the literature. Although some of them may be partially overlaped in some isolates mentioned in the section 5, we demonstrated examples of their sources described in details (Table 5).

7. PATHOGENIC FACTOR(S) OF *C. lari*

Although it is very important to study any bacterial pathogenic factor(s) in order to clarify the pathogenisity of *C. lari*, almost no those reports on *C. lari* have appeared. When Johnson and Lior performed complete toxigenicity studies on 341 strains of *Campylobacter* spp. including 23 nonhuman isolates, toxin profiles based on both cytotonic and cytotoxic factors were determined after analyzing responses in Vero, HeLa, CHO and Y-1 cells. In conclusion, toxigenicity of two *C. lari* human isolates was $CYTOX^{+}$ $CYTON^{+}$, whereas toxigenicity of two nonhuman isolates of *C. lari* (seagulls and bovine feces) was $CYTOX^{+}$ $CYTON^{+}$ and the other two (healthy monkey and sick seal) was $CYTOX^{+}$ $CYTON^{-}$ (Johnson and Lior, 1986). Thus, *C. lari* strains were apparently demonstrated to produce cytotoxic and cytotonic factors.

Table 4. Summary of the clinical isolation of urease-negative *Campylobacter lari*

Country	Year	Disease	Age (Sex)	No. of strains	References
The USA	1984	Bacteremia	71(m)	1	Nachamkin et al., 1984
The USA	1985	Enteritis, severe crampy abdominal pain and terminal bacteremia	71(m), 39(f), 22(f), 7(f), 3(m), 8-month(f)	6	Tauxe et al., 1985
Canada	1985	Enteritis and diarrhea	32(m)	1	Simor and Wilcox, 1987
Canada	1985	Gastroenteritis	NK	7	Broczyk et al., 1987
Australia, Victoria	NK	Gastroenteritis	NK	3	Coloe et al., 1986
Germany	1985-1986	NK (infected humans)	NK	5	Bar et al., 1989
France	NK	Diarrhea	NK	1	Darbas et al., 1987
Italy	NK	Bacteremia in diarrheic AIDS	NK	1	Dionisio et al., 1989,1991
Australia	1988-1989	Diarrhea	<5	2	Albert et al., 1992
Chile	NK	NK	NK	1	Fernandez et al., 1990
Sweden	NK	Gastroenteritis	42(m)	1	Soderstrom et al., 1991
England, Plymoth	1991	NK	NK	6	Guant and Piddock, 1996
Belgium	NK	Diarrhea	NK	13	Eyers et al., 1993
England and Wales	1981-1991	Bacteremia	NK	2	Skirrow et al., 1993
Argentina, Rosario	1985-1993	Acute diarrhea	NK(child)	1	Notario et al., 1996
The USA	1992	Colitis in AIDS	32(f)	1	Evans and Riley, 1992
Spain	1992	HIV infection and diarrhea	NK	1	Reina et al., 1992
Spain	NK	HIV infection and bacteremia	NK	1	Vargas et al., 1992

Table 4 continued….

Taiwan	NK	Chronic diarrhea and bacteremia	neonate(m)	1	Chiu et al., 1995
The Netherlands	NK	Reactive arthritis and enteritis	17(m)	1	Goudswaard et al., 1995
Malaysia	NK	NK	NK	3	Tay et al., 1995
Taiwan	1994-1998	Enteritis	NK	16	Lin et al., 1998
France	1995	Purulent pleurisy	80(m)	1	Bruneau et al., 1998
England and Wales North	NK (two years)	Acute gastroenteritis	NK	1	Lawson et al., 1999
west England and Wales	1997	Diarrhea	NK	25	Thwaites and Frost, 1999
USA	NK	Pacemaker infection and bacteremia	83(f)	1	Morris et al., 1998
France	1999	Bacteremia	90(m)	1	Godreuil et al., 2000
France	1999	Bactermia	10(f)	1	Martinot et al., 2001
France	1995-1999	Infection (stool)	NK	9	Martinot et al., 2001
France	1995-1999	Infection (blood)	NK	1	Martinot et al., 2001
India	NK (over a 12-year period)	Diarrhoea	NK	2	Prasad et al., 2001
New Zealand	NK	Prosthetic joint infection and bacteremia	81(m)	1	Werno et al., 2002
Austria	NK	Recurrent septicemia	75	1	Krause et al., 2002

NK, not known; m, male: f, female

Table 5. Examples of human clinical urease-negative *Campylobacter lari* strains employed for identification and discrimination

No. of isolates	Strain code	Reference
5	729、3331/BC1135、8351/HAM17735、8222/NFLD 33482/85、9160/ALTAE7181	Giesendorf et al., 1993
6	LMG9889 (Canada)、LMG9913、LMG8845(faeces)、LMG9914 (Canada)、LMG11760 (Canada, 1990)、R-1189 (faeces, Belgium)	Duim et al., 2001
16		Meinersmann et al., 2002
3	LMG7607、LMG11760 (Canada)、LMG14338 (Belgium)	Gorkiewicz et al., 2003

8. CONCLUSION

The present review article demonstrates that *C. lari* is a potential human pathogen of gastroenteritis, diarrhea, septicaemia, bacteremia, and is a risk factor for severe disease, even in the immunocompetent host. The natural environment including wild birds and some domestic animals, mainly poultry, have been demonstrated to be important reservoirs of *C. lari*. Although some UPTC isolates have been identified from humans, any association of UPTC with human disease still remains unclear. The differential profiles of association with human disease among *C.* jejuni, *C. lari* and UPTC described above may be resolved mainly by the comparative investigations on phenotypic and genotypic characterization of their virulence determinants appendages (polar flagella and pilus) and toxins (enterotoxins, cytotoxins and so on).

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