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ORIGINAL ARTICLE

Increased incidence of *Campylobacter* enteritis and their quinolone resistance between 2010 and 2015: Results of a French national observatory conducted in 21 general hospitals (CHG)



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KEYWORDS

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Summary

Introduction: In Europe, the number of cases of *Campylobacter* enteritis and their quinolone resistance is increasing. The aims of this work were to evaluate: (1) the hospital epidemiology of bacterial enteritis between 2010 and 2015. (2) The proportion of *Campylobacter* and *Salmonella* enteritis. (3) Resistance to quinolones in adult and paediatric populations. (4) To investigate possible regional epidemiological and bacteriological disparities.

Patients and methods: This is a multicentric study carried out in 21 general hospitals (CHG) representing 14 French regions with a prospective collection of the results of coprocultures from 2010 to 2015 in adult and paediatric populations (children < 15 years old not exposed to quinolones). The epidemiological and bacteriological data were collected from software laboratory for positive stool cultures for *Campylobacter* and *Salmonella*. The results were compared year by year and by a period of 2 years.

Results: In adults, *Campylobacter* enteritis was each year significantly more frequent than *Salmonella* ($P < 0.001$), with a significant increase from 2010 to 2015 ($P < 0.05$). In children, there was also a significant and stable predominance of *Campylobacter* enteritis over the study period ($P = 0.002$). The quinolone resistance of *Campylobacter* was greater than 50% on the whole territory, with no North-South difference over the three periods studied. It increased significantly from 2012 to 2015 in adults (48% to 55%, $P < 0.05$) and in children (54% to 61%, $P = 0.04$).

Conclusion: Our results confirm the increase in the prevalence of *Campylobacter* enteritis compared to *Salmonella* between 2010 and 2015. The quinolone resistance of *Campylobacter* is greater than 50% on the whole territory, stable between 2010 and 2015 in adults and significantly increased in children.

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Introduction

In most industrialized countries, *Campylobacter* infection is the most common cause of foodborne bacterial gastroenteritis [1,2]. This preponderance of enteritis *Campylobacter* is probably underestimated because of the usually benign

nature of the disease, low physician awareness to prescription coprocultures, *Campylobacter* growing difficulties and finally, by its non-systematic search by the laboratories.

The main routes of human transmission of this zoonotic bacterium are the consumption of contaminated meat (mainly poultry) consumed raw or insufficiently cooked

and the cross-contamination of food products consumed raw contaminated by the infected foodstuffs [3]. The evolution of *Campylobacter* enteritis is usually benign but digestive (toxic megacolon, perforation, haemorrhage) [4,5] and extra-digestive complications (mainly secondary extra-digestive infectious site bacteraemia) may, however, occur [6,7]. In addition, *Campylobacter jejuni* is the leading cause of Guillain-Barré Syndrome (GBS), 15 to 45% of GBS being secondary to bacterial infection and one *Campylobacter* enteritis in 1000 is complicating neurological syndrome. Some authors suggest a link between the severity of GBS and the severity of bacterial enteritis [8–10].

In the case of acute dysenteric syndrome suggestive of bacterial colitis, many authors recommend an empirical treatment with quinolones pending the results of coprocultures in order to cover *Salmonella* infections. In France, the number of cases of enteritis with *Campylobacter* and their resistance to quinolones is constantly increasing [11].

To date, no study in the hospital population has been carried out in France. The aims of our study were to evaluate the hospital epidemiology of *Campylobacter* enteritis between 2010 and 2015, the proportion of *Campylobacter* and *Salmonella* enteritis, the resistance to quinolones in adult and paediatric populations, and to investigate the eventual regional in epidemiologic and bacteriologic disparities.

Patients and methods

This is a retrospective multicenter study conducted in 21 general hospitals (CHG) distributed on French territory and representing 14 regions. The participating CHG were the following; Dunkerque and Valenciennes in the region of Hauts de France, Cherbourg in the region of Normandy, Saint-Brieux and Vannes in the region of Bretagne, Cholet and La Roche sur Yon in the region of Pays Val de Loire, Bayonne and Pau in the region of Nouvelle Aquitaine, Perpignan in occitanie, hyères and Aix en Provence in the region of Provence Alpes Cote d’Azur, Montelimar and Annecy in the region of Auvergne-Rhône Alpes, Colmar in region of Grand Est, Orléans in the region centre Val de Loire and Bry sur Marne, Marne la Vallée, Meaux and Montfermeil in the region Ile de France. Epidemiological and bacteriological data were collected prospectively from 2010 to 2015 using laboratory software. Prospective data collection in the laboratories software has allowed obtaining an exhaustive epidemiological and biological data in each participating center. All of the positive stool cultures (except *Clostridium difficile*) in adult and paediatric populations were included for analysis. The paediatric population was represented by children aged less than 15 years who were not exposed to quinolone. The data collected were; age and sex of the patient, date of coprocultures, type of bacterium isolated, antibiotic susceptibility test for *Campylobacter* and *Salmonella* identified. The results were then compared year by year and by a period of 2 years (2010–2011, 2012–2013, 2014–2015).

Statistical analysis was based on the analysis of qualitative variables. The qualitative variables were expressed by their percentage. The comparison of their modalities was performed using Chi² test with a significance level of 0.05.

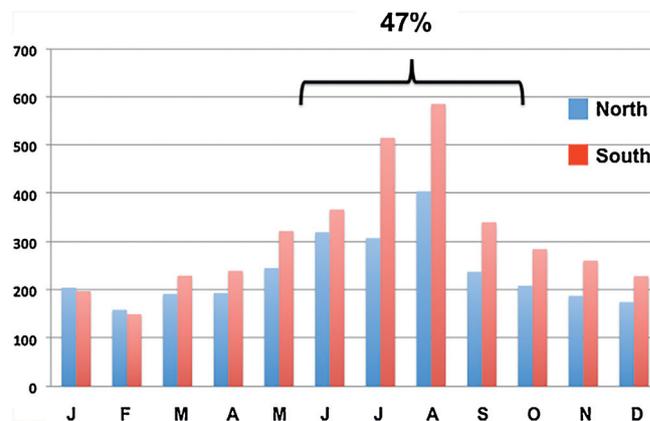


Figure 1 Distribution of the number of *Campylobacter* strains according to the month of sampling, France 2010–2015.

Results

Of the 149,946 co-procultures studied between 2010 and 2015, 4.5–8% were positive depending on the regions, among which 5,103 *Campylobacter* infections (2394 in children and 2709 in adults) and 2709 *Salmonella* infections (1660 in children and 1049 in adults). *Campylobacter* and *Salmonella* enteritis were predominantly predominant, accounting for 74–97% of adult positive coprocultures and 88–99% of child positive coprocultures. The 3 main other identified bacteria were *Shigella*, *Yersinia*, *Klebsiella*.

Seasonal variations in incidence of *Campylobacter* enteritis

Seasonal recrudescence of *Campylobacter* isolates was noted during the summer period, with 47% of infections occurring between June and September. This peak incidence was observed throughout the country with a more marked peak in the South than in the north (Fig. 1). Although less marked than for *C. jejuni*, seasonality was also noted for *C. coli*.

Variations in the incidence of *Campylobacter* enteritis according to age in the adult population

In our adult population, a peak incidence of *Campylobacter* infections was noted in younger adults (16–25 years), followed by a gradual decrease in incidence with age and then a second peak incidence in subjects older than 75 years ($P < 0.0001$). This age-related incidence kinetics was observed in the North and South without significant differences (Fig. 2).

Campylobacter strains isolated

The 2 main strains of *Campylobacter* isolated were *jejuni* and *coli*. *C. jejuni* accounted for 79% to 95% of *Campylobacter* infections and was significantly more frequent than *C. coli* representing 5% to 21% of infections ($P < 0.001$). This predominance of *C. jejuni* was observed in all regions but the ratio *jejuni* / *coli* was less important in some regions such as

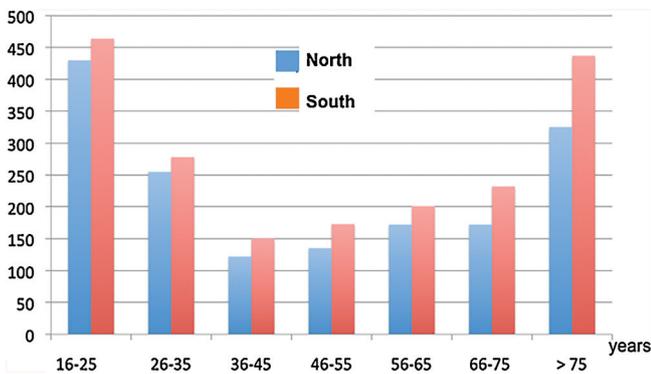


Figure 2 Distribution of *Campylobacter* infections in the adult population according to age in the North and South.

the South West (Pau and Bayonne), the region of Orleans and Ile-de-France, the *C. jejuni* infections representing respectively 61%, 71%, 57% and 68% of *Campylobacter* infections.

Evolution of the incidence of *Campylobacter* and *Salmonella* enteritis from 2010 to 2015

At the national level

In the adult population, for each year studied, *Campylobacter* enteritis was significantly more frequent than *Salmonella* in the whole country (66% in 2010, 70.7% in 2011, 69.9% in 2012, 69.5% in 2013, 77.6% in 2014, 73.4% in 2015) ($P < 0.001$). A progressive but not significant increase in the incidence of *Campylobacter* enteritis was noted from year to year (except from 2013 to 2014), this increase is significant between 2010 and 2015 (66 to 73.4%) ($P < 0.05$). The rate of *Salmonella* infections remained broadly stable during the study period. Thus, from year to year, an increase in the *Campylobacter*/*Salmonella* ratio was noted due to an increase in the incidence of *Campylobacter* enteritis whereas that of *Salmonella* enteritis remained stable.

Table 1

In the paediatric population, it was also noted for each year studied, a significant predominance and, unlike the adult population, stable over time of the incidence of *Campylobacter* enteritis compared to *Salmonella* (57.2% in 2010, 54.9% in 2011, 59.2% in 2012, 57.9% in 2013, 65.5% in 2014, and 58% in 2015) ($P = 0.002$). This *Campylobacter*/*Salmonella* ratio was stable during the follow-up period, outside a significant isolated increase in the rate of *Campylobacter* infections from 2013 to 2014 (57.9% to 65.5%) ($P = 0.003$). In children, the *Campylobacter*/*Salmonella* ratio was lower than in adults, mainly due to the greater number of *Salmonella* enteritis. As in adults, the number of *Salmonella* enteritis remained relatively stable throughout the follow-up. [Table 2](#)

At the regional level

In the last period 2014-2015 of the study, a prevalence of *Campylobacter* infection was noted in all regions in the adult and paediatric populations, except in children in Occitan and Pays de Loire. Indeed, in these two regions, there was a predominance of *Salmonella* enteritis compared to *Campylobacter*, respectively 53.4% and 52%.

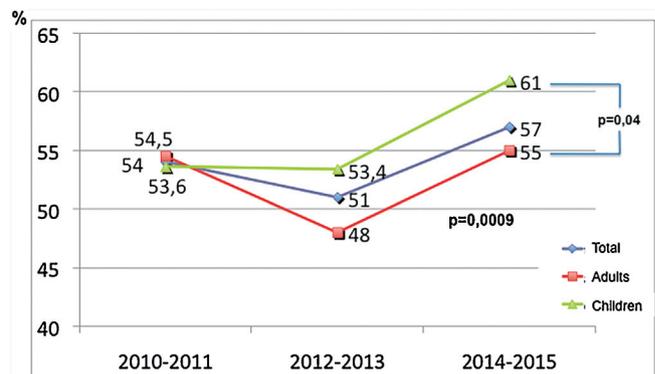


Figure 3 Evolution throughout the French territory from 2010 to 2015 of the resistance rate of *Campylobacter* to quinolones in adult and pediatric populations.

In adults, a significant increase of *Campylobacter* infections between 2010–2011 and 2014–2015 in the Aquitaine-Limousin-Poitou-Charentes region (55% vs. 73.5%; $P = 0.003$) and in the Centre Val de Loire region (62% vs. 77.8%, $P = 0.02$) was noted. In children, a significant increase in *Campylobacter* infections was noted between 2010–2011 and 2014–2015 in Occitania (31% vs. 46%, $P = 0.04$), Aquitaine-Limousin-Poitou-Charentes (37% vs. 65.3%, $P < 0.00001$) and the Hauts-de-France (58% vs. 75%, $P = 0.002$). [Table 3](#)

During the 3 study periods, the incidence of *Salmonella* enteritis was stable in the North and in the South, while an increase in *Campylobacter* enteritis was observed in the North and in the South. This increase is significant in the South between 2010–2011 and 2014–2015 ($P = 0.0002$). In children, the same findings were made in the North, while in the South, there was a decrease in *Salmonella* enteritis and a significant increase in *Campylobacter* enteritis in the period 2014–2015 ($P < 0.00001$).

Evolution of resistance of *Campylobacter* to quinolones

At the national level

The resistance rates of *Campylobacter* to quinolones from 2010 to 2015 were greater than 50% for the entire territory in adult and paediatric populations. In adults, the resistance rates were stable during the 3 study periods (54.5% for 2010–2011 to 55% for 2014–2015) and for children, it was noted a significant increase (53.6% for 2010–2011 to 61% over 2014–2015, $P = 0.0009$) ([Fig. 3](#)). In the last period of 2014–2015, the resistance rate of *Campylobacter* to quinolones was significantly higher in children than in adults, respectively 61% and 55% ($P = 0.04$).

In the adult and paediatric populations, there was no significant difference in the 3 periods of study between resistance rates in the North and in the South. For the period 2014–2015, the rate of resistance to *Campylobacter* quinolones was significantly higher in children than in adults in the North (62% vs. 55%; $P = 0.04$) and in the South (61% vs. 55%; $P = 0.05$).

Table 1 Evolution of the prevalence of *Campylobacter* and *Salmonella* enteritis between 2010 and 2015 throughout France in the adult and paediatric population.

		2010 % (n)	2011 % (n)	2012 % (n)	2013 % (n)	2014 % (n)	2015 % (n)
Adults	<i>Campylobacter</i>	66 (324) ^a	70.7 (439) ^a	69.9 (449) ^a	69.5 (502) ^a	77.6 (589) ^a	73.4 (624) ^a
	<i>Salmonella</i>	34 (166)	29.3 (182)	30.1 (193)	30.5 (221)	22.4 (170)	26.6 (226)
Children	<i>Campylo</i>	57.2 (347) ^b	54.9 (432) ^b	59.2 (421) ^b	57.9 (436) ^b	65.5 (458) ^b	58 (403) ^b
	<i>Salmonella</i>	42.8 (259)	45.1 (355)	40.8 (290)	42.1 (317)	34.5 (241)	42 (291)

^a $P < 0.001$.^b $P = 0.002$.**Table 2** Evolution by region from 2010 to 2015 of ratio of *Campylobacter*/*Salmonella* in adult populations.

Regions	2010–2011(%)	2012–2013(%)	2014–2015(%)
Provence-Alpes-Côte d'Azur	74.7	76.1	77.2
Auvergne-Rhône-Alpes	59.5	73.9	75.5
Aquitaine-Limousin-Poitou Charentes	55 ^a	70.5	73.5 ^a
Occitanie	55	50	60
Bretagne	77.4	69.4	76.7
Pays de Loire	61	58	69
Grand Est	83.3	81.4	82.3
Hauts de France	66	69	75.6
Centre-Val de Loire	64.9 ^b	67.5	77.8 ^b
Ile de France	70.7	75.6	74.3
Normandie	66.6	61	79.5

^a $P = 0.003$.^b $P = 0.02$.**Table 3** Evolution by region from 2010 to 2015 of ratio of *Campylobacter*/*Salmonella* in pediatric populations.

Regions	2010–2011(%)	2012–2013(%)	2014–2015(%)
Provence-Alpes-Côte d'Azur	61.6	58.9	70.9
Auvergne-Rhône-Alpes	51.8	57	60.9
Aquitaine-Limousin-Poitou Charentes	37 ^a	64	65 ^a
Occitanie	32 ^c	35.6	46.6 ^c
Bretagne	55.7	62.7	50.6
Pays de Loire	47	43	48
Grand Est	78.9	75.4	65.4
Hauts de France	56.4 ^b	81.4	74.8 ^b
Centre-Val de Loire	73.5	74.1	78.6
Ile de France	60.6	65	58
Normandie	68	29	62

^a $P < 0.001$.^b $P = 0.002$.^c $P = 0.04$.

At the regional level

It was noted in adults, a significant increase of resistance rates in the PACA region of 2011–2012 to 2014–2015 (43% vs. 61%, $P = 0.03$), Aquitaine Poitou Charentes from 2010–2011 to 2014–2015 (48% vs. 55.7%, $P = 0.007$) and Ile de France from 2010–2011 to 2014–2015 (43% vs. 61%, $P = 0.01$). In children, there was a significant increase of the resistance rate from 2012–2013 to 2014–2015 in the Hauts-de-France region (51% vs. 81%, $P = 0.002$).

Discussion

The results of our study confirm the overall increase in the prevalence of *Campylobacter* enteritis in France between 2010 and 2015. *Campylobacter* infection is the leading cause of bacterial enteritis in adults and in children in the hospital, before the *Salmonella* enteritis. Moreover, the resistance of *Campylobacter* to quinolones is greater than 50% in the whole country, stable in adults between 2010 and 2015

(55%) and increasing in children between 2010 and 2015 (54% at 61%). These results could lead us to change our daily practice by providing first-line empiric treatment with macrolide rather than quinolones in case of acute bacterial enteritis. This predominance of *Campylobacter* enteritis is noted in the North and in the South of France and represents about 3/4 of infections in adults (74% *Campylobacter* vs. 26% *Salmonella*) and 2/3 of infections in children (64% *Campylobacter* versus 36% *Salmonella*). However, there is an exception in Occitania and in the Pays de Loire region where *Salmonella* infections remain the most frequent. The predominance of *Salmonella* enteritis in children in these regions is very likely multifactorial and could be explained, at least in Occitania, by the fact that *Salmonella* is a bacterium linked to the rupture of the cold chain.

In most industrialized countries, the incidence of *Campylobacter* infections has increased in recent years and has become the leading cause of acute bacterial diarrhea before salmonellosis [12,13].

Campylobacter reservoir is the digestive tract of homeothermic animals, especially production animals such as domestic birds (chicken, turkey, duck...) and mammals (cattle, pigs, small ruminants). The main transmission paths to humans are the consumption of contaminated raw or undercooked foodstuffs and the manipulation of contaminated products in the kitchen, contributing to the spread of *Campylobacter* to food intended for raw consumption, to work surfaces or kitchen utensils and finally, to the hands of users [3].

Poultry meat is to date the most frequently and heavily contaminated meat with bacteria, approximately 40% of batches being contaminated with *C. jejuni*, 29.7% with *C. coli* and more than 2% with of the 2 species. As a result, poultry meat in general and chicken in particular, represent the majority of human infections on all continents, as has been confirmed in many epidemiological studies [14,15]. In poultry breeding, the introduction of *Campylobacter* via a breakdown of sanitary barriers remains the main cause identified, the bacteria remain in the digestive tract of birds at high rates throughout the breeding period. The risks of digestive soiling of the carcass during slaughter, particularly during the evisceration stage, by transferring the bacteria from the digestive reservoir of the animals to the surface of the muscular masses, are very high in these conditions. Bacteria can survive throughout the production chain to the consumer's kitchen, and even for storage temperatures corresponding to those of the cold chain (from -20°C to 10°C). The increased incidence of *Campylobacter* enteritis can be explained by poor hygiene at every stage of the food chain, at farms level, slaughterhouses, workshops for processing meat and ultimately the consumer in the kitchen.

Our results concerning the epidemiological data are identical to those already reported in the literature [16]. There is a seasonal variation in contamination with recrudescence of *Campylobacter* isolates during the summer period. Indeed, 47% of cases were reported between June and September, this increased incidence summer being noted in the North and in the South of France. Several studies [17,18] have shown that the incidence of human campylobacteriosis and the colonization of poultry flocks followed a similar seasonal evolution and that both were highly correlated with outdoor temperatures. Baumgartner et al [19] have shown that

poultry flocks contamination levels were higher during the summer months with a contamination with larger amounts of bacteria.

In the adult population, two peaks of incidence of *Campylobacter* enteritis was found, the first in young adults, followed by a gradual decrease in incidence and second in the elderly over 75 years. The first peak of incidence in young adults could be explained by a different feeding behaviour with greater consumption of poultry, the progressive decrease following the peak by the acquisition of protective immunity secondary to repeated exposures to the bacteria [20], and the second peak in the elderly by a decrease in immune defenses which may contribute to lowering the infestation thresholds.

Throughout the French territory, a clear prevalence of *Campylobacter jejuni* compared to *C. coli* (80% versus 20%) was also noted. The predominance of *C. jejuni* is less pronounced in the southwest of France (Pau, Bayonne), the regions Center-Val de Loire and in Ile-de-France, without any clear explanation. This difference may be related in these regions to disparities in eating habits, poultry supply chains.

In our study, the rate of resistance of *Campylobacter* to quinolones was greater than 50% throughout the territory, and this for the adult and paediatric populations. The quinolone resistance rate was relatively stable in adults between 2010 and 2015, around 55%, but there was a significant increase in children between 2010 and 2015 to 61% in 2015. This high level of resistance in our paediatric population aged under 15 years, not exposed to quinolones because contraindicated in children, is in favour of resistance linked to the use of antibiotics in industrial farms and not to prior exposure of patients. Indeed, antibiotics can be used in animal husbandry as a veterinary drug and as a growth factor. Anti-biotics are used in farms with curative aim in case of proven infection in the animal, with a metaphylactic aim, generally consisting of large-scale industrial farms, if contagious infection reported in a sufficient number of animals (usually 10 to 15%), to treat all animals and finally; with a prophylactic aim, For prophylactic purposes, by treating non-diseased animals which are exposed to a risk factor exposes them to a high probability of developing a disease in the short term. Furthermore, the use of antibiotics as a food additive and growth factor improves zootechnical performance preventing the nutrients ingested by the animal to be used by the commensal bacteria of the intestine, which act as competitors. Antibiotics used as growth factors are used at very low concentrations, the aim is not to systematically eliminate bacteria, but rather to maintain a constant concentration of antibiotics in order to permanently influence the intestinal microbiota. Thus, the antibiotics used to improve the efficiency of microbial digestion and allow a significant reduction in the amounts ingested for the same weight gain and thus to increase the growth rate of the animals. These, therefore, induce a selection pressure for antibiotic resistance in bacteria of animal origin, especially those constituting the intestinal flora.

The development of this resistance brings about several types of risks, the first concerns the veterinarian, leading to the failure of treatments in animals, the second is the selection of zoonotic bacteria resistant to antibiotics prescribed in humans, the third is the constitution of a reservoir of resis-

tance genes capable of being transported to man via food or the environment.

The increased resistance of *Campylobacter* to quinolones has been observed in recent years in countries where the frequency of use of these antibiotics in animals is much higher (Spain, China, United States). In France, the national reference center for *Campylobacter* and *Helicobacter* has recorded a gradual increase in resistance to quinolones since 2004 to reach 56.9% for ciprofloxacin in 2015, and even 65.8% for the *C. coli* [16]. The same findings have been made in Europe, notably in the Netherlands [21] and in Spain [22]. Conversely, countries that have banned the use of these antibiotics in farm animals, such as Australia, or use them sparingly, such as Sweden, have very low levels of resistance to quinolones.

The results of our study confirm the high levels of resistance to quinolones of *Campylobacter* in children and adults and suggest that in case of bacterial enteritis, a probabilistic antibiotic therapy by macrolide is preferable to a first-line antibiotic therapy with quinolones, given the high incidence of *Campylobacter* enteritis and their high rate of resistance to quinolones. Indeed, according to data from the national reference center published in 2015, *Campylobacter*'s resistance to macrolides is 1% versus 35% for ampicillin and 50% for tetracyclines [16].

The strengths of our work are its multicentric character with 21 hospitals covering the entire French territory and the prospective data collection using laboratory software allowing the completeness of epidemiological and bacteriological data. The weaknesses of the study are the lack of a participating hospital center in certain French regions (especially in the center) and the lack of clinical data, which cannot be obtained with laboratory software.

In conclusion, our results confirm the overall increase in the prevalence of *Campylobacter* enteritis in France between 2010 and 2015, infection with *Campylobacter* representing the first cause of hospital-acquired bacterial enteritis in adults and children, before *Salmonella* enteritis. Furthermore, the resistance of *Campylobacter* to quinolones is greater than 50% on the whole territory, stable in adults between 2010 and 2015 (55%) and increasing in children between 2010 and 2015 (54% to 61%). This high rate of resistance in our paediatric population is in favour of resistance linked to the use of antibiotics in industrial farms and not to prior exposure of patients. These results should motivate to enhance the education of the population, farmers and veterinarians on hygiene measures at each stage of the food chain and to ensure good practices for the appropriate use of antibiotics in animal husbandry

Specific author contributions

- 1 Study concept and design;
- 2 acquisition of data;
- 3 analysis and interpretation of data;
- 4 drafting of the manuscript;
- 5 critical revision of the manuscript for important intellectual content;
- 6 statistical analysis;
- 7 technical or material support;
- 8 study supervision.

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Disclosure of interest

The authors declare that they have no competing interest.

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