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# A Cosmopolitan One Health Issue: Campylobacteriosis

**Massimo Giangaspero***

*Faculty of Veterinary Medicine, University of Teramo, Italy*

***Corresponding author:** Massimo Giangaspero, DVM, MSc, PhD, Faculty of Veterinary Medicine, University of Teramo, Italy, E-mail: giangasp@gmail.com

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**Abstract**

In Europe, since 2005, campylobacteriosis is considered among the most frequent cause of bacterial gastrointestinal infectious disease. The diffusion is cosmopolitan, accounting for an increasing global burden on public health, affecting primarily children under 4 years of age, causing gastroenteric symptoms, but also different extra intestinal pathologies. The infection appears associated also with malnutrition and growth impairment in disadvantaged communities. The consumption of contaminated poultry meat is considered to be the most frequent way of transmission. The progressive diffusion and increase of antibiotic-resistant *Campylobacter* strains is an issue, particularly in South America and Southeast Asia. Effective regulatory approaches are necessary at national and international level by both sanitary and veterinary authorities to counter such serious zoonosis, in the spirit of One Health.

**Keywords:** *Campylobacter*; Infectious disease; One health

## Introduction

Campylobacteriosis is among the most diffuse infectious diseases of the last decades. The prevalence has particularly increased everywhere, independently from medicalization status, in both developed and developing countries. In regions of Africa, Asia, and the Middle East the infection is endemic in particular among infants. In Europe, since 2005, the infection due to thermotolerant *Campylobacter* spp. in humans become more frequent than that caused by *Salmonella* spp., representing the most common reported infectious gastrointestinal pathology [1]. According to the European Centre for Disease Prevention & Control (ECDC) surveillance report of 2011, based on data from the European Surveillance System (TESSy), in Europe *Campylobacter* spp. infection was responsible for 178,000 cases in 2006 and accounted for up to 202,000 cases (53.07 per 100,000) in 2009. In 2012, the notified confirmed cases were 212,000. In Germany, Hungary and UK highest number of cases (up to 60,000) have been reported. Also in Switzerland, in 2009, campylobacteriosis resulted the most frequent bacterial zoonosis, with more than 8,000 reported cases (100.1 per 100,000) [2], inducing the establishment of the *Campylobacter* platform, an active monitoring plan at national level. Studies revealed particularly alarming estimations, as up to 500,000 cases per year in the United Kingdom [3]. *Campylobacter jejuni* and *C. coli* are the two species mainly isolated in man, especially during summer months. In 2009, *C. jejuni* was the most frequently reported species (36.4%). The other species *C. coli* (2.5%), *C. lari* (0.19%) and *C. upsaliensis* (0.01%) were rarely isolated from patients. But many of the isolates from the other confirmed cases (51%) could not be characterized. The health problem is cosmopolitan, for example, also in the United States campylobacteriosis in humans is one of the most common pathogens responsible for foodborne disease. According to data obtained through the active surveillance system ensured by the Foodborne Diseases Active Surveillance Network (FoodNet), every year, about 14 cases are diagnosed for each 100,000 persons in the population (6.033 notified cases in 2009). But the Centres for Disease Control and Prevention (CDC) estimated that the infection affects yearly more than 1.3 million patients, since many cases are supposed to go undiagnosed or unreported to public health authorities [4].

Campylobacteriosis is a zoonosis. Various domestic and wild animal species can host the bacterium and they act as natural reservoirs. The role of domestic avian species in the epidemiology of the disease in humans is well known. Domestic avian species are the main reservoir and source of transmission of *Campylobacter* spp. to man, often in relation with high levels of contamination in poultry meat [5,6]. Humans become infected through contact with animals and their products, such as avian meat and raw milk. The consumption of contaminated poultry meat not sufficiently cooked is considered to be the most frequent way of transmission. Often, contaminations are indirect occurring during manipulations of food for cooking in the in the kitchen environment, through stoves or other kitchen utensils utilized without precautions contemporaneously with raw meat and for other food.

The impact on public health is considered high, being associated with 7.5 million disability-adjusted life years according to the 2010 Global Burden of Disease Study, more than *Shigella* (7.1 million) and enterotoxigenic *E. coli* (6.9 million) [7]. On the base of fragmentary studies, the prevalence of *C. jejuni* and *C. coli* reported in relation with diarrhoea in human population from different countries, in South America showed rates ranging from 9.6% in Brazil and up to 41.3% among infants suffering from gastroenteritis in Peru [8,9] or 84.9% among infants of less than 6 months of age in Brazil and Peru [10].

In humans, symptoms are mainly gastroenteric. Few bacteria are sufficient to determine violent abdominal pain and diarrhoea. Both *C. jejuni* and *C. coli* may provoke enteritis in all age categories. But, most affected result to be infants under four years of age, as shown by epidemiological data reported in 2009 (144.34 per 100,000) [1]. In particular, *C. jejuni* can cause various extra intestinal forms. This includes bacteremia, meningitis, peritonitis, pancreatitis, cholecystitis, cystitis and urethritis, neonatal sepsis, abortion, endocarditis, osteomyelitis, septic thrombophlebitis, septic arthritis, as well as immunomediate chronic forms like nodous erythema. *C. jejuni* is also suspected in the etiopathogenesis of Guillain Barré the post infective neurological syndrome and the rare variant Miller-Fisher syndrome. The similarity between bacterial lipopolysaccharides and gangliosides might be at the origin of an auto-immune reaction [11-13]. Furthermore, recent studies indicate an association between *Campylobacter* infection and malnutrition, caused by an induced intestinal and systemic chronic inflammation, with a subsequent perturbation of the growth, in low resourced communities, particularly evident also in Peru [10]. Nevertheless, the impact of *C. jejuni, C. coli,* and non-*jejuni/coli Campylobacter* strains in children, in particular living in the developing countries, constitute a threatening reality, even if greatly underestimated and largely undiagnosed. Among non-*jejuni/coli Campylobacter*, there is an emerging recognition of the clinical importance of *Campylobacter* species as *C. concisus* and *C. ureolyticus*. Less frequently isolated in poultry, both species are suspected to be associated with Crohn's disease and ulcerative colitis in man [14-16]. The mortality rate associated with *Campylobacter* infection seems generally low (0.05 per 1,000 cases) [12]. It is not excluded that infection related mortality may also be higher and not negligible, as suggested by some studies. For example, mortality in relation to confirmed cases in the Netherlands, in 2008, accounted for 45 deaths out of 3,340 patients, and in 2010 deaths were 58 out of 4,322 cases [17].

Despite increasing importance for public heath, in veterinary medicine, monitoring of *Campylobacter* is often incomplete. In Switzerland, the 44% of poultry samples were positive mainly to *C. jejuni*. In pigs the 67% was positive, but with almost all for *C. coli*. Only the 1% of tested calves resulted positive to both *C. jejuni* and *C. coli* [2]. *Campylobacter* is often detected in poultry meat [6]. For example, high contamination percentages have been found in UK (71%) [5] and Italy (81.3%) [18]. In South America too, high contamination levels have been reported. In Brazil, 66.9% of live poultry and 68.8% of poultry meat resulted positives to *C. jejuni* [19,20], while among cattle positive were 53.3% [21]. Reacting to the rising importance of campylobacteriosis, the European Commission financed a first monitoring program in the poultry sector to determine prevalence and levels of antibiotic resistance [22]. As in other countries, in Italy, this funding allowed to undertake extended epidemiological investigations, revealing high prevalence of *Campylobacter* in avian meat. The 72.3% of slaughter lots were positive, with percentages of positivity in carcasses up to 71.5% and 75.8% in Veneto and Marche regions, respectively [23]. The 52.1% of characterized isolates were *C. jejuni*; *C. coli* represented the 55.6% and *C. lari* 1.1%. Very high levels of contamination, e.g. >10,000 unit forming colonies (UFC)/g, have been also detected. Among wild animal species potential reservoirs of *Campylobacter*, avian families are most frequently infected, mainly crows (*Corvidae*) and gulls (*Laridae*) with the highest carriage rates of *C. jejuni*: 23%-89.8% and 25%-50%, respectively [24,25]. In Italy were reported positive rates of 34.1% and 38.8 % [26,27].

Animals are generally, asymptomatic carriers of *Campylobacter* spp.. However, in wild animals, occurrence of gastroenteritis related with *Campylobacter* was described in different animal orders: Artiodactyla 15%, Galliformes 15%, Anseriformes 30%, Ciconiformes 34% and Gruiformes 44% [28]. In addition, *C. jejuni* was reported to be associated with pathologies affecting various species such as mink (*Mustela vison*) suffering from colitis, severe diarrhea, abortion and death, or severe diarrhea in in primates and raccoon (*Procyon lotor*), and enteritis and hepatitis in ostrich (*Struthio camelus*).

Currently, the prevention of campylobacteriosis relies mainly on general hygienic approaches. Preventive measures in food safety have to be applied at all the levels of the food chain from primary production up to distribution retail, and not neglecting good hygienic practices at household, recognized also relevant aspects. The World Health Organization (WHO) has developed policies for the promotion and strengthening of food safety systems, good practices in the manufacturing sector as well as education of food business operators and consumers on appropriate food handling in order to avoid cross contamination. Risk communication, through education of consumers and training of food handlers is among the most critical interventions to prevention foodborne illnesses [29]. To reduce the prevalence of *Campylobacter* in poultry, it is necessary to enhance biosecurity measures at farm level to avoid introduction of *Campylobacter* from the environment. Similarly, safe disposal of faeces and articles soiled with faeces is particularly important in countries without adequate sewage disposal systems. This requires closed housing conditions, despite preferable free ranging farming for animal welfare. The application of good hygienic practices during slaughtering will ensure the reduction of the contamination of carcasses by faeces, but they will not guarantee the complete elimination of *Campylobacter*, thus, meat and meat products will maintain a certain risk level. Few methods, such as heating (e.g. cooking or pasteurization) or irradiation, are effective to eliminate *Campylobacter* in contaminated foods [29]. In low resource settings, the reduction of the burden of *Campylobacter* infection for the improvement of growth in children can be achieved through the promotion of breastfeeding, avoiding the use of potentially contaminated water for the preparation of maternal milk substitution, adequate treatment of drinking water, improved hygiene of latrines, and targeted antibiotic treatment, avoiding the use of known antibacterials with demonstrated resistance among *Campylobacter* strains [10].

The high level of contamination of food of animal origin is the primary issue. It has been estimated that the reduction of the 90% of the cases of human campylobacteriosis could be achieved by limiting contamination levels under 500 UFC per gram in raw poultry meat [2]. Therefore, it should be a priority objective to reduce the bacterial burden of raw meat to radically decrease the impact of the infection on public health. To date, vaccination of chickens against *Campylobacter* is still at experimental level, but with preliminary promising results [30]. Pathogen reduction treatments (PRTs), such as physical treatments with temperature or pression or chemical compounds as chlorate solutions, can efficiently reduce the burden of pathogens from the surface of the meat when applied on poultry carcasses at the end of the slaughtering process [31,32]. But, only the use of lactic acid as PRT in plants processing bovine meat has been recently authorized by the European Union (EU) [33]. All other practices are not permitted according to the enforced European food law [34]. Such legal diverging framework caused long term disputes between EU and USA sanitary veterinary administrations [35]. It will be therefore interesting to drive research efforts focused on alternative means for the achievement of the objective to reduce contamination levels, and taking into account that application of current hygienic measures during slaughtering and subsequent evisceration does not effectively prevent contamination of meat surface from bacteria present in the intestinal contain.

Of particular importance, it is the increasing number of reports on *Campylobacter* strains resistant to different antibiotics, not only in Europe [36,37], but also and especially in Southeast Asia and South America. After the substantial increasing of resistance to quinolones and fluoroquinolones during the last decade [38], resistance to macrolides has been more and more described, as Azithromycin in India and Peru [39,40]. In Latin America, various studies demonstrated the circulation of particularly high number of isolates of resistant *Campylobacter* spp.. In Brazil, up to 72.2% of isolates were resistant to quinolones, up to 43% to tetracycline, or up to 38.9% to erythromycin and up to 26.9% for ampicillin [41-43]. Very high percentages (47-78%) of strains resistant to quinolones have been described also in Argentina, Bolivia, Chili and Peru; as well as from 40.8% to 65.9% for tetracycline in Argentina and in Bolivia; from 58.6% to 61.4% for erythromycin in Bolivia and Chili, or 47.2% for ampicilline in Argentina [44-49]. These observations indicate the generality of the problematic also in this continent. In particular, this phenomenon highlights the high risk of the direct relation between resistance of strains isolated in man and utilisation of these molecules in veterinary medicine in particular in the poultry sector, and this even after years since the enforcement of the ban in EU and USA of the non-therapeutic use of antimicrobials in domestic animals, as enrofloxacin in poultry farms [50,51]. Love and collaborators [50] demonstrated high percentages of inhibitory levels of forbidden quinolones in poultry feathers, with the risk of their reintroduction in the food chain through fertilization or animal feeding. This suggests that the ban as now applied does not seems to prevent exposure of poultry to the molecules known to induce antibiotic resistant *Campylobacter*. In addition, the use of antimicrobials as fluoroquinolone, for prophylaxis or growth promotion in farmed animals, is still permitted in many developing countries, and cheaper generics can increase these practices.

Campylobacteriosis is relevant for the “One Health” concept, based on the idea that human health and animal health are interdependent. This concept, introduced at the beginning of the 2000s, was envisaged and implemented by the World Organization for Animal Health (Office International des Épizooties: OIE) as a collaborative global approach to understanding risks for human and animal health. However, in veterinary medicine, legal norms formulated for *Campylobacter* spp. are probably insufficient and enforcement in the field appears problematic. Generally, animals are asymptomatic carriers of *Campylobacter* spp., the silent infection is widespread and endemic in the zootechnic sector, and this may explain the apparent low reactivity against the infection by the farmers, probably also related with inadequate risk communication. Practically, no obligation of declaration or restriction to distribution and commercialization of affected live animals and contaminated food of animal origin are implemented.

Campylobacteriosis has been included among diseases submitted to rules for the prevention and control in Annex II of the EU Regulation 429 [52]. However, at international level it is compulsorily reportable only for bovine genital campylobacteriosis [53], while not contemplated among diseases of avian species, thus, not relevant for international trade rules of animals and animal products according to World Trade Organization’s Sanitary and Phytosanitary agreements (WTO SPSS). For example, when compared to other zoonotic pathogens circulating in Europe or exotic, such as *C. burnetii* (Q fever) or Nipah virus (NiV), *Campylobacter* appears to be much less important to the NiV, most dangerous agent (Table 1).

In fact, due to the significant morbidity and mortality, and rapid spread potential in domestic animals, and evidence of zoonotic properties, recently, Nipah virus has been included in the list of diseases with relevance for international trade of the World Organization for Animal Health (OIE) [53]. In NiV non-endemic countries scientific attention is high on henipaviruses, and practical regulatory field implications foreseen that NiV outbreaks have to be immediately notified to OIE by the veterinary authority. In contrast, despite the recognized importance taking into account the very high incidence in human population, inclusion of *Campylobacter* in national veterinary monitoring plans remains questionable and prioritization may drive the attention to other pathogens showing for example higher health impact in the animal population.

| **Pathogen** | *Campylobacter* **spp.** | *C. burnetii* | **Nipah Virus** |
|---|---|---|---|
| OIE notifiable disease | Bovine diseases genital campylobacteriosis | Multiple species diseases Q Fever | Pig diseases Nipah virus encephalitis |
| Zoonosis | YES | YES | YES |
| Pathogenicity in man | + | + | +++ |
| Therapeutic or prophylactic means | YES | YES | NO |
| Risk Category | 2 | 2 | 4 |
| Domestic animals | YES | YES | YES |
| Wild animals | YES | YES | YES |

**Table 1:** Comparison between *Campylobacter* spp. and other zoonotic pathogens. NiV appears to be the most dangerous agent. Risk category classification according to the Italian National Committee for biosafety and biotechnology and life sciences [54].

## Conclusion

In conclusion, knowledge and awareness on the disease should be harmonized, improved and disseminated among health services, veterinarians, farmers and consumers. Taking into account that *Campylobacter* is considered to be the most common cause of bacterial gastroenteritis worldwide, this One Health issue will need to be dealt with on an international scale, trough harmonized sanitary and veterinary regulatory measures.

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