

Campylobacter – A Foodborne Pathogen

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Abstract: *Campylobacter* is well recognized as the leading cause of bacterial food borne diarrheal disease worldwide. Symptoms can range from mild to serious infections of the children and the elderly. The organism is a cytochrome oxidase positive, microaerophilic, curved Gram-negative rod exhibiting cork screw motility and is carried in the intestine of many wild and domestic animals, particularly avian species including poultry. Intestinal colonization results in healthy animals as carriers. In contrast with the most recent published reviews that cover specific aspects of *Campylobacter/campylobacteriosis*, this broad review aims at elucidating and discussing (i) genus *Campylobacter*, growth and survival characteristics (ii) detection, isolation and confirmation of *Campylobacter* (iii) *campylobacteriosis* and presence of virulence factors (iv) Clinical features in special set-up, antimicrobial susceptibility pattern.

Keywords: *Campylobacter* spp., food borne pathogens, virulence factors, antimicrobial susceptibility, control measures.

1. Introduction

It is believed that the first report concerning *Campylobacter* was back in 1886 by The Escherich who observed and described non-culturable spiral-shaped bacteria.[1] After this, *Campylobacter* was identified for the first time in 1906 when two British veterinarians reported the presence of “large numbers of a peculiar organism” in the uterine mucus of fetuses. Later in 1927, Smith and Orcutt named a group of bacteria, isolated from the feces of cattle with diarrhea, as *Vibrio jejuni*. Seven-teen years later, in 1944, Doyle isolated a different vibrio from feces of pigs with diarrhea and classified them as *Vibriocoli*. [1] Due to their low DNA base composition, their non-fermentative metabolism and their microaerophilic growth requirements, the genus *Campylobacter* was first proposed in 1963 by Sebald and Véron, distinguishing them from the “true” *Vibrio* spp. After that, the study of Butzler et al. (1973) raised the interest in *Campylobacter* by noting their high incidence in human diarrhea.[3] Since its inception, the taxonomic structure of the genus *Campylobacter* has experienced extensive changes and even some parts of the current genus taxonomy remain a matter of controversy and require further investigation.[4] According to these latter authors, Debruyne et al.(2005), there are 14 validly described *Campylobacter* species. More recently, Fernández et al. (2008) stated that the genus comprises 20 species and subspecies.[5] However, other authors have stated that there are 16 species with a further six subspecies within the genus *Campylobacter*. *Campylobacter*'s have been known to be the cause of diseases in animals since 1909, but they have been generally recognized as a cause of human disease, only since about 1980.[6]

2. General characteristic of *Campylobacter*

The family *Campylobacteraceae* consists of two genera, *Campylobacter* and *Arcobacter* and occurs primarily as commensals in humans and domestic animals.[7]

The genus name *Campylobacter* was derived from the Greek word for curved rod. It was proposed by Sebald and Veron to

include microaerophilic bacteria that were different from *Vibrio cholerae* and other vibrios in a number of respects.[8] *Campylobacter* are gram-negative bacteria 0.5 to 8 µm long and 0.2 to 0.5 µm wide with characteristically curved, spiral, or S-shaped cells (Figure 1). They generally have a single polar unsheathed flagellum (monotrichous) or a flagellum at each end (amphitrichous). One species, *C. pylori*, has one to six sheathed flagella located at one end of the cell. [9,10] The motility of the bacteria is characteristically rapid and darting in corkscrew fashion, a feature by which their presence among other bacteria can be detected by phase-contrast microscopy.[11] Their guanine-plus-cytosine (G+C) content is low, ranging from 28 to 38 mol%. [12,13] Biochemical reactions by which *Campylobacter* species may be differentiated are relatively few because of their inability to ferment or oxidize the usual carbohydrate substrates available in the diagnostic laboratory. They have are



Figure 1: Secondary gram stain of *campylobacter* spp

spiratory type of metabolism and use amino acids and intermediates of the tricarboxylic acid cycle. They are oxidase positive and reduce nitrates. The catalase test is one of the few useful tests for differentiating the species. The genus is currently in a state of flux. New species are being defined at a rapid pace, while at least one species, *C. pylori*, is being considered for reassignment to another genus. Descriptions of new species have been difficult because the number of discriminatory characteristics still remain few. In a number of instances species differ more in the degree to

which a characteristic is demonstrable than in number of different characters. As pointed out by Neill et al.,[14] with respect to atmospheric conditions, there exists a spectrum for optimal growth extending from the anaerobic requirements of some species to the natural oxygen tolerance of another, *C. cryaerophila*. Most species are microaerophilic, lying between these two extremes. Similarly, there is a wide range in the temperatures for culturing bacteria, extending from 150C for *C. cryaerophila* to 41 to 420C for *C. jejuni*, *C. coli*, and *C. laridis*. Moreover, species and individual strains vary in tolerance of growth temperatures from the temperatures considered optimum. While *C. fetus* subsp. *fetus* grows at 250C and can be cultured at 370C, some strains have been isolated at 420C .[15] Inhibitory tests introduced to differentiate species have not been spectacularly successful because of the wide tolerance variability among individual strains of the same species. In some cases, species differentiation has been based on the degree of inhibition by the same compound rather than on that by a number of different compounds. As a result, different concentrations of the inhibitory materials are used for characterization of species, making the construction of a classification scheme for the genus as a whole somewhat cumbersome. To illustrate, the range of concentrations of sodium chloride that have been used to test for growth inhibition includes 1.5 ,[16,17] 2.0 ,[18,19,14] 3.0 ,[20] 3.5 ,[16,17,21,22,23,24,], and 4.0%.[25] Furthermore, the more reliable genetic tests for differentiation cannot be readily performed in the clinical laboratory. *Campylobacter* species vary immensely in their habitats. Some (e.g., *C. pylori*) appear to be obligate parasites restricted narrowly to one organ or site in the body, while others (e.g., *C. jejuni*) are widely distributed in nature, evoking the term "ubiquitous" to describe their habitat. In at least one case (*C. fetus* subsp. *venerealis*), the source of the isolate is as reliable a taxonomic criterion for the bacterium as are the tests for identification that may be performed subsequently in the laboratory. It has been observed in other cases that, soon after a species was described, isolates were found that would be excluded from the species if the criteria used to define the species were rigorously applied. It is not surprising, therefore, that species identification in the genus *Campylobacter* has drawn attention to the importance of the genetic constitution of the strain as the final criterion in taxonomy. The deoxy ribonucleic acid (DNA)-DNA hybridization technique can certainly be credited with rescuing the genus from the state of confusion that could be anticipated if taxonomic decisions were based solely on phenotypic traits.

3. Incidence

Generally, developing countries do not have national surveillance programs for campylobacteriosis; therefore, incidence values in terms of number of cases for a population do not exist. Availability of national surveillance programs in developed countries has facilitated monitoring of sporadic cases as well as outbreaks of human campylobacteriosis.[26,27-30] Most estimates of incidence in developing countries are from laboratory-based surveillance of pathogens responsible for diarrhea. *Campylobacter* isolation rates in developing countries range from 5 to

20%.[31] Despite the lack of incidence data from national surveys, case-control community-based studies have provided estimates of 40,000 to 60,000/100,000 for children <5 years of age.[31,32] In contrast, the figure for developed countries is 300/100,00 .[27] Estimates in the general population in developing and developed countries are similar, approximately 90/100,000 ,[27,31,33] confirming the observation that campylobacteriosis is often a pediatric disease in developing countries. The isolation and incidence rates in some developing countries have increased since their initial reports.[34] This increase has often been attributed to improved diagnostic methods, but an actual increase in incidence was observed in *Campylobacter*-associated diarrhea in the Caribbean island of Curaçao .[35]

4. Age of Infection

In developing countries, *Campylobacter* is the most commonly isolated bacterial pathogen from <2-year-old children with diarrhea .The disease does not appear to be important in adults. In contrast, infection occurs in adults and children in developed countries. Poor hygiene and sanitation and the close proximity to animals in developing countries all contribute to easy and frequent acquisition of any enteric pathogen, including *Campylobacter*. Although infections in infants appear to decline with age , a comprehensive community-based cohort study in Egypt has shown that infection could be pathogenic regardless of the age of the child, underscoring the need for strengthening prevention and control strategies for campylobacteriosis .[36]

5. Polymicrobial Infections Involving *Campylobacter*

Campylobacter is isolated relatively frequently with another enteric pathogen in patients with diarrhea in developing countries. In some cases half or more patients with *Campylobacter* enteritis also had other enteric pathogens.[37,38] Organisms reported include *Escherichia coli*, *Salmonella*, *Shigella*, *Giardia lamblia*, and *Rotavirus*. Polymicrobial infections involving *Campylobacter* are rare in developed countries.[31,33]

6. Seasonal Variation

In developing countries, *Campylobacter* enteritis has no seasonal preference; in contrast, in developed countries epidemics occur in summer and autumn.[26] Isolation peaks vary from one country to another and also within countries. [36,39,40]The lack of seasonal preference may be due to lack of extreme temperature variation as well as lack of adequate surveillance for epidemics. [31, 33]

7. Species of the genus *Campylobacter*(Table 1)

The genus *Campylobacter* currently includes 14 species. Some species are in quotation marks, indicating that they were proposed but have not been validated by publication in the International Journal of Systemic Bacteriology or by inclusion in the lists of new names published outside that

journal. A convenient practice in the past has been to divide the species into two groups based on catalase production. This originated with veterinarians [25] who found that the test permitted differentiation of *C. fetus*, the bovine pathogen of interest, from commensals now classified as *C. sputorum* biovar *bubulus*.

This grouping continued into the last decade [23] but has become less relevant since the newly described nonpathogenic species *C. cryaerophila* and *C. nitrofigilis* are also catalase positive. *C. jejuni* and *C. coli* have been referred to as the thermophilic group of campylobacteria, but *C. laridis* and "*C. upsaliensis*" are also thermophilic. *C. hyointestinalis* may also be considered thermophilic, but perhaps it would be more appropriate to regard this species as thermotolerant because it grows more abundantly at 37°C than at 42°C. [41] In contrast, "*C. cinaedi*" and "*C. fennelliae*" grow at 37°C but not at 25 or 42°C. H₂S production based on the use of triple sugar iron agar (TSI) is presented in Table 1 in preference to other methods because the medium has been used to test strains of all species except *C. nitrofigilis* and also because experience with Enterobacteriaceae has shown that there are fewer contradictory results with TSI than with tests with lead acetate paper strips. [42] Edmonds et al. [43] observed positive H₂S tests for six species of *Campylobacter* with lead acetate strips, but only two species were positive when TSI agar was used.

Three groups of investigators [12,23,44] are in agreement that H₂S is not detected in *C. jejuni*, *C. coli*, and *C. laridis* when the TSI medium is used. Of the armamentarium of biochemical tests available to the clinical microbiologist, the ones for detecting H₂S production are perhaps the most notable for causing confusion. A review of the complexities of the reactions involved in H₂S production from chemically undefined media and the contradictory results that may arise have been discussed in an elegant review by Barrett and Clark [42] Two enzymes, cysteine desulfhydrase and thiosulfate reductase, produce H₂S from cysteine and thiosulfate, respectively. Problems arise because media in diagnostic tests vary in thiosulfate and peptone content. Variation in cysteine content of the peptones can also be expected. Moreover, lead acetate reacts with volatile thiols as well as with H₂S, whereas iron used in TSI apparently reacts only with H₂S. However, a medium that gives reproducible results and permits the definition of biotypes has been designed for campylobacteria by Skirrow and Benjamin. [45] This medium contains ferrous sulfate, sodium metabisulfite, and sodium pyruvate and has been found useful for biotyping thermophilic campylobacteria in at least three laboratories. [23,45,46] With this medium, *C. jejuni* biotype 2

and *C. laridis* strains are H₂S positive, whereas *C. jejuni* biotype 1 and *C. coli* strains are H₂S negative. A new test included in table 1 is the hydrolysis of indoxylacetate as described by Mills and Gherna. [47] Although its applicability in the clinical laboratory has not been confirmed by others and not all species have been tested, it nevertheless offers promise as a useful test for differentiation among the species of the thermophilic group and between "*C. cinaedi*" and "*C. fennelliae*." The classification of Roop et al. [17] has been used for *C. sputorum* and *C. mucosalis*. The significant changes introduced by these workers include the recognition of *C. sputorum* subsp. *mucosalis* as a species and the separation of *C. sputorum* into three biovars, one of which is biovar *fecalis*, formerly considered to be a separate species known as "*C. fecalis*." Except for the hippurate test, reactions or properties distinct for a particular species have not warranted a separate column, but some should be mentioned. Yellow-pigmented colonies are a characteristic feature of *C. mucosalis*. Urease is produced by *C. pylori* and *C. nitrofigilis*. *C. nitrofigilis* also produces nitrogenase and from tryptophan it produces a brown pigment. *C. cryaerophila* grows at 37°C, but the optimum growth temperature is 30°C and all strains grow at 150°C. *C. cryaerophila* after isolation will grow anaerobically, in air, or in air containing 10% CO₂. "*C. fennelliae*" colonies have a distinctive odor of hypochlorite

8. Pathogenesis of *Campylobacter*

8.1 virulence factors

Specific virulence mechanisms have not yet been clearly elucidated for *Campylobacter* spp. probably due to the lack of pathogenesis similarity between campylobacters and other pathogens. [48] Flagella-mediated motility, bacterial adherence to intestinal mucosa, invasive capability and the ability to produce toxins have been identified as virulence. [49] Despite the limited knowledge of the modus operandi of this pathogen, it is known that flagella are required for the colonization of the small intestine; after that it moves to the target organ, which is the colon. [50] Invasion, which causes cellular inflammation, is probably resulting from the production of cytotoxins, and is followed by the reduction of the absorptive capacity of the intestine. [51] It is thought that the ability of this pathogen to reach the intestinal tract is, in part, due to resistance to gastric acids and also to bile salts, [51] even though the disease severity may depend on the virulence of the strain as well as on the host's immune condition. [2]

Table 1: Differential reactions and characteristics for species of the genus *Campylobacter*

Species	Reactions and characteristics												
	Catalase	Nitrate	H ₂ S (TSI)	Hippurate	Indoxyl acetate	Growth			Susceptibility ^c		G+C content (mol%)		
						25°C	37°C	42°C	1% Glycine	0.1% TMAO (anaerobic)		Nalidixic acid	Cephalothin
<i>C. fetus</i> subsp. <i>fetus</i>	+	+	-	-	-	+	+	(-)	+	-	R	S	33-34
<i>C. fetus</i> subsp. <i>venerealis</i>	+	+	-	-	-	+	+	-	-	-	R	S	33-34
<i>C. hyointestinalis</i>	+	+	+	-	-	(+)	+	+	+	+	R	S	35-36
<i>C. jejuni</i>	+	+	-	+	+	-	+	+	+	-	S	R	30-32
<i>C. coli</i>	+	+	-	-	+	-	+	+	+	-	S	R	31-33
<i>C. laridis</i>	+	+	-	-	-	-	+	+	+	+	R	R	31-33
" <i>C. upsaliensis</i> "	(-)	+	-	-	ND	-	+	+	-	-	S	S	35-36
" <i>C. cinaedi</i> "	+	+	-	-	(-)	-	+	-	+	-	S	I	37-38
" <i>C. fennelliae</i> "	+	-	-	-	+	-	+	-	+	-	S	S	37-38
<i>C. cryaerophila</i>	+	+	-	-	+	+	+	-	-	ND	d	R	29-30
<i>C. nitrofigilis</i>	+	+	ND	-	-	+	+	-	-	ND	S	S	28-29
<i>C. sputorum</i>													
Biovar <i>sputorum</i>	-	+	(+)	-	-	-	+	+	+	d	(S)	S	31-32
Biovar <i>bubulus</i>	-	+	+	-	-	-	+	+	+	+	R	S	31-32
Biovar <i>fecalis</i>	+	+	+	-	-	-	+	+	+	+	R	S	32-33
<i>C. mucosalis</i>	-	+	+	-	-	+	+	+	+	-	R	S	38-39
<i>C. concisus</i>	-	+	+	-	ND	-	+	+	+	-	R	R	38-39
<i>C. pylori</i>	+	d	-	-	-	-	+	+	d		R	S	36-37

8.1.1 Flagella

Motility, which increases under highly viscous conditions, is essential for colonization of the small intestine.[52] Moreover, the role of flagella under different chemotactic conditions is essential for bacterial survival in the various ecological niches encountered in the gastrointestinal tract.[52]

The *C. coli* flagellum is composed of two highly homologous flagellins, FlaA which is the major one, and FlaB the minor one .[48] These are encoded by two flagellin genes arranged in tandem. The flaA gene is regulated by promoter σ_{28} while flaB gene is regulated by the dependent promoter σ_{54} .[52] The flaA gene seems to be essential for the invasion of epithelial cells, since it has been reported that a mutation in this gene leads to a truncated flagellar filament composed of flaB with a severe reduction in its motility .[48] However, a mutation in flaB appears to have no significance compared with a structurally normal flagellum . The flaA gene is responsible for the expression of adherence, colonization of the gastrointestinal tract and invasion of the host cells .[53] consequently arresting the immune response. In fact, it is believed that flagella possess another characteristic which is the ability to secrete non-flagellar proteins that may be associated with the virulence phenomenon itself .[50] *C. jejuni* possesses a polar flagellum that is composed of O-linked glycosylated flagellin; a two-component system comprised of the sensor FlgS and the response regulator FlgR is central for the regulation of the *Campylobacter* flagellum. [49]

8.1.2 Cytolethal distending toxin

Cytolethal distending toxin (CDT) is widely distributed among Gram-negative bacteria [54] and is the best characterized of the toxins produced by *Campylobacter* spp.

It has been described as an important virulence factor of this pathogen .[55] CDT holotoxin, composed of three subunits encoded by the *cdt A*, *cdt B* and *cdt C* genes, causes eukaryotic cells to arrest in the G2/M phase of the cell cycle, preventing them from entering mitosis and consequently lead-ing to cell death.[2] In contrast to CdtB, the roles of CdtA and CdtC are still rather unclear and require further investigation ,[56] partly because these proteins tend to combine with the bacterial outer membrane which probably causes cross-contamination . [57] Despite this, CdtA and CdtC are thought to be essential for CdtB delivery into the host cell, being responsible for binding the CDT holotoxin to the cell membrane. After that, the CdtB active subunit, which has DNaseI-like activity, induces host DNA damage by breaking its double strand .[54]

In fact, to be functionally active, all three *cdt* gene products must be present .[57] *Cdt* genes have already been cloned and/or sequenced for *C. jejuni* [58] and more recently for *C. coli* and *Campylobacter fetus* .[55] According to some authors, the *cdt* gene clusters are ubiquitously distributed in *C. jejuni*, *C. coli*, and *C. fetus* in a species-specific manner .[58]

9. Detection, Isolation and Confirmation

The sensitivity of *Campylobacter* spp. to oxygen and oxidizing radicals has led to the development of several selective media containing one or more oxygen scavengers, such as blood, ferrous iron, pyruvate, etc., and selective agents, particularly antibiotics. Most methods involve a pre-enrichment in a liquid medium, before plating on agar. The developments of methods for *Campylobacter* have been well-described by Corry et al. (1995).[59]

In some protocols, in order to ameliorate the inhibitory effects of the selective agents on potentially damaged cells,

initial suspension of samples is made into a basal broth without selective agents, with the latter being gradually added after a short period of incubation. In order to permit recovery of damaged cells, the incubation temperature may also be gradually increased from 37°C to the final incubation temperature of 41.5°C. This methodology is the basis for one of the ISO standard methods [60,61] However, for chicken samples, such a protocol was not necessary as maximal numbers were obtained by using a selective broth followed by plating on selective agars [62] *Campylobacter* spp. Show typical characteristic grow on Blood Agar as show in Figure 2



Figure 2: Growth of campylobacter sponn Blood Agar

Several of the selective broths, e.g., Bolton broth (BB), *Campylobacter* enrichment broth (CEB), and Preston broth (PB), have been compared for their efficacy [63] The incorporation of the enzyme Oxyrase in selective broths is particularly effective in reducing the levels of oxygen and improving the isolation of *Campylobacter* spp. from naturally contaminated samples [64] However, a blood free enrichment broth not requiring the addition of Oxyrase, nor special atmospheres has been tested and found to perform well against other more complex isolation methods [65] Several selective agars have been formulated and tested for their efficacy in isolating campylobacters. For example, Preston, charcoal cefoperazone deoxycholate (CCDA) and Butzler agars have been found to be equally effective. The use of CCDA and incubation at 42°C rather than 37°C is usually the methodology of choice since it allows for the isolation of more *Campylobacter* strains [66] Corry and Atabay (1997)[67] developed CAT agar from modified CCDA by altering the levels of the antibiotics to permit growth of a wider range of strains of *Campylobacter* spp., notably *Campylobacter upsaliensis*. A later comparison by Federighi et al. (1999), [68] of Karmali, Butzler, and Skirrow isolation agars after enrichment of a large number and wide range of samples in Preston or Park and Sanders broths, showed that Park and Sanders broth followed by isolation on Karmali agar was the more effective combination. The most recent standard method [61] for detection and isolation, and a direct plating method for enumeration of campylobacters [69] both use mCCDA as the selective agar. Bolton broth is used for the enrichment step and the suspension is incubated at 37°C in a microaerophilic atmosphere for 4–6 h, followed by 41.5°C for 40–48 h and plating on mCCDA and another agar medium of the operator's own choice. However,

methods for *Campylobacter* spp. are not commonly used in routine laboratories as the organisms are difficult to cultivate and to keep reference cultures.

Several alternative and rapid methods have been developed for detecting and confirming *Campylobacter* spp. e. g. those that include fluorescence in situ hybridization [70] latex agglutination (commercially available; e.g., Wilma et al., 1992; Microscreen® *Campylobacter* kit), and a physical enrichment method (filtration) that permits the separation of *Campylobacter* from other organisms present in the food matrix [71] Perhaps the most effective confirmation methods are those based on the polymerase chain reaction (PCR) reaction, since the phenotypic reactions are often atypical and difficult to read, e.g., the hippurate hydrolysis test for differentiating *Campylobacter coli* from *C. jejuni*. The PCR reaction has been combined with immune-separation with some success [72] in detecting low numbers of the organism in only about 6 h. However, some components of both food samples and selective broths can be inhibitory to the PCR reaction. More recently real-time PCR methods have been developed that show the potential of detecting as few as 1 cfu in chicken samples, and in less than 2 h [73] Epidemiological studies (e.g., outbreak investigations) have been benefited from the use of molecular typing techniques such as PCR, random amplification of polymorphic DNA (RAPD) and pulsed field gel electrophoresis (PFGE).

Clinical Features

The clinical spectrum of *Campylobacter* enteritis ranges from a watery, non bloody, non inflammatory diarrhea to a severe inflammatory diarrhea with abdominal pain and fever. Disease is less severe in developing countries than in developed countries (5,6). In developed countries, disease is characterized by bloody stool, fever, and abdominal pain that is often more severe than that observed for *Shigella* and *Salmonella* infections. In developing countries the features reported are watery stool, fever, abdominal pain, vomiting, dehydration, and presence of fecal leukocytes; patients are also often underweight and malnourished (12,31,51). In Lagos, Nigeria, *Campylobacter* enteritis is characterized by a history of watery offensive-smelling stool lasting <5 days (51)

10. *Campylobacter* as a Cause of Traveler's Diarrhea

Travel to a developing country is a risk factor for acquiring *Campylobacter*-associated diarrhea. The diarrhea is more severe, and strains are associated with antibiotic resistance.

11. *Campylobacter* Infection in the Setting of HIV

Campylobacter-associated diarrhea and bacteremia occurs HIV/AIDS patients worldwide. The species isolated include *C. jejuni*, *C. coli*, *C. upsaliensis*, *Arcobacter butzleri*, *Helicobacter fennelliae* and *H.cinaedii* [74,75] The incidence of clinical manifestations is higher than in HIV-

negative patients, with substantial mortality and morbidity. Furthermore, antibiotic resistance and recurrent infections have been observed.[76] The incidence of HIV/AIDS is higher in developing countries than in developed countries and contributes substantially to deaths among <5-year-old children in epidemic settings.[77] Thus, infants in developing countries are at risk of impaired immunity to *Campylobacter* enteritis. In addition, HIV/AIDS can increase the number of cases of campylobacteriosis in the adult population in these countries. These observations further support the need for improved understanding of the epidemiology of campylobacteriosis in developing countries.

12. Immunologic Aspects

In developing countries, such as Bangladesh, Thailand, Central African Republic, and Mexico, healthy children and adults are constantly exposed to *Campylobacter* antigens in the environment. As a consequence, serum antibodies to *Campylobacter* species develop very early in life in children in developing countries, and the levels of such antibodies tend to be much higher than those in children in the developed world such as in the United States. [78] In Nigeria, children who had diarrhea and children who were healthy both had antibodies in their sera that could agglutinate *C. jejuni*; the difference in antibody responses between these groups of children was not statistically significant.[79] Thus, antibody responses alone should be interpreted with caution in diagnosing *Campylobacter* infections. In spite of shortcomings in the use of antibodies for diagnosis, increase in the level of anti-flagellar antibody had an inverse correlation with the rates of *Campylobacter* enteritis in the Central African Republic.[80] An age-related relationship in the development of immunity to *campylobacter* antigens has also been suggested to account for the age-related declines in the case-to-infection ratio and the period of excretion during the convalescent phase.[81,82] Usually, as age increases, level of antibody tends to increase. At the earliest stages in life (first 6 months), immunoglobulin (Ig) A, IgG, and IgM levels in response to *Campylobacter* infection are minimal, but thereafter increases are observed in response to infection. The poor serologic response during the first 6 months of life may be due either to a primary response to *Campylobacter* or to the presence of maternal

antibodies via the placenta or breast milk. Breast-feeding has been reported to play a role in *C. jejuni* induced diarrhea. It decreases the number of episodes and the duration of diarrhea.[83] In Algeria, exclusively breast-fed infants had fewer symptomatic *Campylobacter* infections than infants who were both breast-fed and bottle-fed.[84] In the developed world, the epidemiology may be different because most cases are usually primary infections with more severe clinical manifestations, greater numbers of people with bloody diarrhea (50%, as opposed to 15% in developing countries), and a more prolonged duration of excretion (approximately 15 days, compared with 7 days in developing countries).[81] The widespread immunity seen among adults in developing countries is absent in adults in developed countries.[78]

13. Sources of Human Campylobacteriosis

Campylobacter infection is hyperendemic in developing countries. The major sources of human infections are environmental contamination and foods. Human-to-human transmission as a result of prolonged convalescent-phase excretion and high population density have also been suggested,[33,36] although observations from developed countries show these are less likely factors.[26] Foods *Campylobacter*-contaminated foods—the result of poor sanitation—are an important potential source of infection in humans. In developed countries, risk factors associated with foods include occupational exposure to farm animals, consumption of raw milk or milk products, and unhygienic food preparation practices.[26]

14. Antibiotic Resistance in *Campylobacter* Isolates

Campylobacter enteritis is a self-limiting disease, and antimicrobial therapy is not generally recommended. However, antimicrobial agents are recommended for extra intestinal infections and for treating immunocompromised persons. Erythromycin and ciprofloxacin are drugs of choice.[29] The rate of resistance to these drugs is increasing in both developed and developing countries, although the incidence is higher in developing countries. Use of these drugs for infections other than gastroenteritis and self-medication are often the causes of resistance in developing countries; in developed countries, resistance is due to their use in food animals and travel to developing countries. The increase in erythromycin resistance in developed countries is often low and stable at approximately 1% to 2%; this is not true for developing countries.[85,86] For example, in 1984, 82% of *Campylobacter* strains from Lagos, Nigeria, were sensitive to erythromycin; 10 years later, only 20.8% were sensitive.[34] In addition, resistance to another macrolide, azithromycin, was found in 7% to 15% of *Campylobacter* isolates in 1994 and 1995 in Thailand.[87] The increasing rate of resistance to the fluoroquinolone, ciprofloxacin limits its clinical usefulness. In Thailand, ciprofloxacin resistance among *Campylobacter* species increased from zero before 1991 to 84% in 1995.[87] Recent data have shown a marked increase in resistance to quinolones in developed countries.[88]

15. Conclusion

The incidence of human campylobacteriosis is increasing worldwide and has attracted the attention of WHO. Substantial gaps in knowledge about the epidemiology of campylobacteriosis in developing countries still exist. When various socioeconomic and health changes in developing countries are taken into account, these values may have changed considerably. Thus, public health awareness about the problem is needed, as are strengthened diagnostic facilities for campylobacteriosis, with a view towards setting up national surveillance programs. Such programs would determine the incidence rates, epidemiologic risk factors, interaction of HIV/AIDS and campylobacteriosis, seasonal

variation, current state of resistance to antimicrobial agents, role of species other than *C. jejuni* and *C. coli*. Collaboration among researchers in developed and developing countries needs to be strengthened, All these should contribute to understanding of the global epidemiology of human campylobacteriosis.

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