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ABSTRACT

Background: *Campylobacter jejuni/coli* is one of the most commonly identified bacterial causes of acute gastroenteritis worldwide. In Nigeria, it has been reported in the northern part of the country, extensive work has also been done in the south-west leaving behind the middle-belt of the country. **Objective:** To determine the role of *Campylobacter jejuni/coli* as an agent of diarrhoea in the middle-belt of Nigeria.

Design: A prospective case control study.

Setting: University of Ilorin Teaching Hospital (UIITH), private hospitals and primary health centers all in Ilorin, Nigeria.

Subjects: Three hundred and six children with diarrhoea and 100 without diarrhoea were randomly selected.

Main outcome measures: Isolation of *Campylobacter jejuni/coli* from stool samples. Biological characteristics of the isolates.

Results: Twenty five (8.2%) of the patients and none of the controls had the organism. *Campylobacter jejuni* and *C. coli* were 56% and 44% respectively. All the isolates were susceptible to erythromycin and ciprofloxacin. None of the isolates harboured plasmids.

Conclusion: *C. jejuni/coli* is an important diarrhoea agent in our geographic environment, further characterisation is desired of these local strains.

INTRODUCTION

Campylobacter spp. have been the focus of growing attention for the past 30 years because of the increasing frequency with which they have been isolated from man, animals, food and water. Although several *Campylobacter* spp. (*Campylobacter jejuni*, *C. coli*, *C. upsaliensis*, *C. lari*, *C. concisus*, *C. fetus* subsp. *fetus*, *Campylobacter jejuni* subsp. *Doylei*, *C. hyointestinalis*) have been shown to cause diarrhoea,

Campylobacter jejuni is by far the most frequent species isolated in man. *Campylobacter jejuni* is a frequent cause of morbidity, in both industrialised and developing countries, and represents a considerable drain on economic and public health resources. In the 1970s, collaboration between medical doctors and their veterinary colleagues led to the discovery of *Campylobacter* enteritis (1). The recent completion of the genome sequence of *Campylobacter jejuni* now promises to open up the

Campylobacter research field with the prospect of developing novel therapeutic and preventive strategies (2).

Campylobacter jejuni/coli are well established causative agents of diarrhoea in Nigeria. Gastroenteritis due to *Campylobacter jejuni* was first reported in the northern part of the country in 1981 (3) and the South-Western part in Ile-Ife in 1983 (4). In 1984, the most comprehensive report on *Campylobacter jejuni* as an agent of diarrhoea particularly in children was given by Coker and Dosunmu-Ogunbi (5,6). Since then, isolation rate of *Campylobacter* spp from cases of diarrhoea in the country has increased and has led to a series of careful biological studies on the local strains (7-12).

Despite the extensive studies in South-West and Northern Nigeria (3-12), there is paucity of information from the middle belt of the country about *Campylobacter jejuni* documenting the role of this organism which has become the most commonly recognised cause of bacterial gastroenteritis in man (1). This present study was undertaken to determine the prevalence and biologic characteristics of *Campylobacter* spp in Ilorin, a semi-urban city in the middle belt of Nigeria.

MATERIALS AND METHODS

Study area: This study was carried out prospectively at the University of Ilorin Teaching Hospital (UITH), Private Hospitals and Primary Health Centres in Ilorin between December 2002 and November 2003. Ilorin is located at the middle belt zone of Nigeria and UITH provides health care services to the people of Kwara State and the neighbouring Kogi, Niger, Oyo, Osun, Ekiti and Ondo States.

Subjects: Subjects were patients between the age of 0 and 36 months, who presented with watery, offensive diarrhoea with or without blood and fever at the Paediatric Unit of University of Ilorin Teaching Hospital, Private Hospitals and Primary Health Centres in Ilorin, Nigeria. A total of 306 patients with diarrhoea and 100 without diarrhoea for the preceding two weeks (as controls) were recruited. They were registered in the project register where basic demographic data about the patients such as name, age, sex, ward etc were recorded. Diarrhoea is defined as passage of three or more loose and watery stool per day.

Ethical Consideration: It was a non-invasive study. However, informed consent was obtained from each of the mothers of all the children. The study was approved by the Ethical and Research Committee of the University of Ilorin Teaching Hospital, Ilorin.

Methods: Rectal swabs and stool samples were cultured directly on Butzler-type medium (5). These were incubated at 37°C in candle extinction jars for 72 hours. In positive specimens characteristic effuse colonies were formed. These colonies were gram stained and showed spiral gram-negative bacteria. Isolates were considered to be *Campylobacter jejuni/coli* if they were motile, oxidase positive, catalase positive, grew at 37°C and 42°C but not at 25°C. All isolates were stored in a medium containing ferrous sulphate, sodium metabisulphite and sodium pyruvate (FBP) and kept frozen. The characterisation of the isolates involving antibiotics susceptibility testing, beta-lactamase production, biotyping and plasmid analysis were performed at Nigerian Institute of Medical Research (NIMR), Lagos.

The Kirby-Bauer disc diffusion method for *in vitro* susceptibility testing (13) was employed in this study. Five colonies of each strain of *Campylobacter* isolate were suspended in a sterile bijou bottle containing 5mls of Mueller-Hinton broth Oxoid Ltd, London, U.K.) and incubated overnight at 37°C. The overnight broth cultures were diluted to 10⁶ colony forming units per ml. Sterile cotton wool swabs were inserted into the standardised inoculum, drained off and then used to inoculate well dried Mueller-Hinton agar plate. The following antibiotic discs (ampicillin 25µg, ciprofloxacin 25µg, gentamicin 10µg, erythromycin 10µg, nalidixic acid 30µg, nitrofurantoin 200µg, ceftriaxone 30µg, colistin 25µg, streptomycin 25µg and tetracycline 25µg) were placed onto the inoculated agar plates. All plates were incubated in candle extinction jars at 42°C for 48 hours. The diameters of zones of inhibition were measured to the nearest millimeter using a ruler. The zones of inhibition of the test strains when comparable with the zones of inhibition of control organisms were interpreted as sensitive, while those showing no zones of inhibition or narrower zones of inhibition than those of sensitive control organisms were interpreted as resistant. The control organism was *Campylobacter jejuni* 11168.

Isolates were biotyped using the Lior typing schemes (14) consisting of rapid hippurate

hydrolysis, the rapid Hydrogen sulphide (H₂S) and DNA hydrolysis tests.

Isolation of plasmids was done by the modified Birnboim and Doly method (15).

RESULTS

A total of 406 subjects were examined during the period of study, 306 (75%) with diarrhoea and 100 (25%) without diarrhoea served as control (Table 1). Out of 306 subjects with diarrhoea, 25 were positive for *Campylobacter species* giving a prevalence rate of 8.2%. The male to female ratio was 1:1. None of the control subjects was positive for *Campylobacter species* (Table 2). The age distribution of children with diarrhoea is shown in Table 3. All the isolates were from children below the age of two years (24 months).

All the isolates were biotyped according to the scheme shown in Table 4. Twelve (48.0%) were *Campylobacter jejuni* biotype I, 2(8.0%) were *Campylobacter jejuni* biotype II and 11(44%) were *C. coli* biotype I. (Table 5).

The antibiotic susceptibility pattern of the isolates is as shown in Table 6. All the isolates (100%) were sensitive to erythromycin and ciprofloxacin and also highly sensitive to gentamycin (96.0%), nitrofurantoin (92.0%), tetracycline (88%), streptomycin (88%), colistin (84%) and nalidixic acid (76.0%). But the isolates were generally resistant to cotrimoxazole (96.0%), ampicillin (68.0%) and ceftriaxone (84.0%). Only one of the isolates (4%) out of 25 produced β -lactamase. None of the isolates (0%) was found to contain detectable plasmid.

Table 1

Sex distribution of patients examined

Number of subjects	M	F	Total
Number with diarrhoea	172	134	306
Number without diarrhoea (controls)	68	32	100
Total	240	166	406

Table 2

Distribution of patients with Campylobacter jejuni/C. coli infection by sex

Sex	Children with diarrhoea			Children without diarrhoea (controls)		
	No. examined	No. positive	(%) positive	No. examined	No. positive	(%) positive
Male	172	13	4.3	68	0	0
Female	134	12	3.9	32	0	0
Total	306	25	8.2	100	0	0

Table 3

Age distribution of patients with Campylobacter enteritis

Age (months)	Children with diarrhoea		
	No. examined	No. positive	(%) positive
0-6	68	3	4.4
7-12	138	13	9.4
13-18	53	6	11.3
19-24	31	3	9.7
25-30	7	0	0
31-36	9	0	0

Table 4
Biotyping scheme for C. jejuni, C.coli and C. laridis

Biotype	<i>C. jejuni</i>				<i>C. coli</i>		<i>C. laridis</i>	
	I	I I	II I	IV	I	II	I	II
Test								
Hippurate Hydrolysis	+	+	+	+	-	-	-	-
Rapid H ₂ S Test	-	-	+	+	-	-	+	+
DNA Hydrolysis	-	+	-	+	-	+	-	+

Table 5
Biotype distribution of isolates

Biotype	No. of Positive	(%) Positive
<i>Campylobacter jejuni</i>		
Biotype I	12	48
Biotype II	2	8
<i>Campylobacter coli</i>		
Biotype I	11	44
Total	25	100

Table 6
Susceptibility rate of the isolated strains to antibiotic agents

Antibiotic	Sensitive strains		Resistant strains	
	No.	(%)	No.	(%)
Cotrimoxazole (25µg)	1	4.0	24	96.0
Ampicilin (25µg)	8	32.0	17	68.0
Nalidixic acid (30µg)	19	76.0	6	24.0
Nitrofurantoin (200µg)	23	92.0	2	8.0
Ceftriaxone (30µg)	4	16.0	21	84.0
Colistin (25µg)	21	84.0	4	16.0
Streptomycin (25µg)	22	88.0	3	12.0
Tetracycline (25µg)	22	88.0	3	12.0
Erythromycin (10µg)	25	100	0	0
Gentamycin (10µg)	24	96.0	1	4.0
Ciprofloxacin (25µg)	25	100	0	0

DISCUSSION

Results of this study have shown that *Campylobacter jejuni/coli* is an important diarrhoeagenic agent in children. The isolation rate is 8.2%. This is the first report about isolation of *Campylobacter jejuni/coli* in the middle belt of Nigeria. Previous rates have ranged from 5.2% (5) through 11% (8) to 16.5% (11)

in Lagos and 12.4% (4) to 19.1% (12) in Ile-Ife both in South-West Nigeria. Reports from developing countries have put the prevalence rate in the range of 5-20% (16) except in Liberia (17) where the isolation rate among children from urban slum and rural areas as 44.9% and 28.4% respectively. The isolation rates contrast with those from developed countries such as Belgium (18), England (19) and

United States (20) where the isolation rates varies between 5.1% and 7.1%. Generally, in developing countries *Campylobacter* infection is hyperendemic owing to poor sanitation and close contact with animals in the home.

Of note is the fact that *Campylobacter jejuni/coli* was not isolated from control children. This finding lends credence that the organisms actually are causative agents of diarrhoea. In fact Coker and Dosunmu-Ogunbi (5,9) had earlier reported that *Campylobacter jejuni/coli* is usually pathogenic.

All the isolates (100%) in this study were obtained from children below the age of two years. This agrees with earlier studies done in the country (9,11) but disagrees with the findings in developed countries where infections tend to occur commonly in adults (21).

Age specific differences in the isolation rate of *Campylobacter jejuni/coli* suggest that the epidemiology of infection is quite different in the developed and developing countries. The infections occur very early in life in the developing countries where *Campylobacter* infections are endemic with peak isolation rate occurring in children less than three years old and associated with a humoral response to *Campylobacter jejuni* antigens (22). *Campylobacter* enteritis does not appear to be an important disease in adults in developing world. The poor standard of hygiene, lack of sanitation and close proximity to animals that prevail in many of these countries are an ideal setting for the easy and frequent acquisition of any enteric pathogen more so, for *Campylobacter* spp. which have been associated with dogs, chickens, sheep and unpasteurised milk. This would account for the higher isolation rate in African children compared to European children and possibly absence of disease in adults. With exposure to hyper endemic infection, there is early acquisition of immunity by the children with rising concentrations of specific antibody especially immunoglobulin A (23,24). Subsequently, infection tends to be asymptomatic or mild in its clinical picture.

In our study we note only a slight male preponderance of (4.3%) against (3.9%) in females. This unlike some other previous studies in south-west Nigeria where it has been shown that infection was more common in males than in females (6,11,12). Likewise in industrialised nations there is a preponderance of males among infected persons which begins during early childhood and persists

until old age (25). The reason for the sex distribution is unknown (26).

Biotyping of our isolates showed more of *Campylobacter jejuni* (56%) than *C. coli* (44%). This pattern correlates with earlier reports over the years in Lagos, Nigeria (8,11,27) where more of *Campylobacter jejuni* compared to *C. coli* have been isolated consistently. However the report of Aboderin *et al* (12) showed more of *C. coli* (53.3%) than *Campylobacter jejuni* (46.6%) somewhere else in South-west Nigeria. This and the fact that we still have a high occurrence of *C. coli* (44%) may suggest that *C. coli* infection is on the increase. In fact many developing countries such as Central African Republic, Chile and Hong Kong, *C. coli* accounts for a higher proportions of infections than elsewhere. Although *C. coli* is particularly associated with pigs, this association is not exclusive, and in some areas *C. coli* is commonly reported in chickens (28).

The development of antimicrobial resistance in the last four decades has led to an intensification of discussion about the prudent use of antimicrobial agents. All the 25 isolates in this study were susceptible to erythromycin and ciprofloxacin. *Campylobacter* enteritis though usually a self-limiting infection, antibiotics may be indicated for treatment of the more severe cases. Erythromycin has been considered the drug of choice for treating *Campylobacter jejuni* gastrointestinal infections and ciprofloxacin, gentamicin and tetracycline are used as alternative drugs (29). The pattern of susceptibility in this study is similar to that of Aboderin *et al* (12) where all isolates were susceptible to erythromycin and ciprofloxacin amongst other agents. Furthermore, Cabrita *et al* (30) did not record any resistance to erythromycin in their isolates. However there are reports of increasing resistance to erythromycin in other places. A high level resistance was reported in Singapore (31), Saudi Arabia (32) and Lagos, Nigeria (8,9,11).

On the other hand, of the 25 isolates, 96% were resistant to cotrimoxazole, 84% to ceftriaxone, 68% to ampicillin, 24% to nalidixic acid, 16% to colistin, 12% to tetracycline and streptomycin. Resistance to nitrofurantoin and gentamicin was 8% and 4% respectively. It is obvious that despite the fact that all the isolates were susceptible to erythromycin and ciprofloxacin, these local strains are still highly resistant to other drugs. In fact high rates of resistance make tetracycline, amoxicillin, ampicillin,

metronidazole and cephalosporins poor choices for the treatment of infections with *Campylobacter jejuni* (26). Even with ciprofloxacin to which all our isolates are susceptible, there is need for caution in its use as there are rapidly increasing proportion of *Campylobacter* strains found to be fluoroquinolone resistant worldwide (27). As *Campylobacter* spp. are considered zoonotic pathogens, resistance among isolates in the animal reservoir could have implications for the treatment of human infections. There is need not only to control antimicrobial use in humans but also in poultry and animals so as to prevent or at least delay development of resistance to these agents. None of the 25 isolates harbour plasmids. This agrees with a previous report from Lagos, Nigeria that human isolates of *Campylobacter* infrequently possess plasmids (33). It is noteworthy though, that some other reports have shown that plasmid determination together with serotyping can be used as an epidemiological tool (34,35).

It is reasonable to conclude that in our geographical area *Campylobacter jejuni/coli* is an important aetiological agent of diarrhoea as the isolation rates compare well with that of other developing countries. Furthermore erythromycin remains the drug of choice for treating human infections; gentamicin and tetracycline can be used as alternative drugs. Ciprofloxacin can be a reserve drug since there is no evidence of resistance yet. The role of plasmid profile determination in epidemiological studies needs further investigation.

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