Human Campylobacteriosis in Developing Countries

Akitoye O. Coker,* Raphael D. Isokpehi,* Bolaji N. Thomas,* Kehinde O. Amisu,* and C. Larry Obi†

Campylobacteriosis is a collective description for infectious diseases caused by members of the bacterial genus *Campylobacter*. The only form of campylobacteriosis of major public health importance is *Campylobacter* enteritis due to *C. jejuni* and *C. coli*. Research and control efforts on the disease have been conducted more often in developed countries than developing countries. However, because of the increasing incidence, expanding spectrum of infections, potential of HIV-related deaths due to *Campylobacter*, and the availability of the complete genome sequence of *C. jejuni* NCTC 11168, interest in campylobacteriosis research and control in developing countries is growing. We present the distinguishing epidemiologic and clinical features of *Campylobacter* enteritis in developing countries relative to developing countries. National surveillance programs and international collaborations are needed to address the substantial gaps in the knowledge about the epidemiology of campylobacteriosis in developing countries.

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 (2,8-11). 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% (6). Table 1 shows isolation rates for some countries according to WHO regions from studies of diarrhea in children <5 years old (14-25). 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 (6,12). In contrast, the figure for developed countries is 300/100,000 (8). Estimates in the general population in developing and developed countries are similar, approximately 90/100,000 (5,6,8), confirming the observation that campylobacteriosis is often a

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1 Portions of this review were presented at the World Health Organization Consultation on the Increasing Incidence of Campylobacteriosis in Humans, Copenhagen, Denmark, November 1-25, 2000. In addition, relevant emerging information from the 11th International Workshop on *Campylobacter*, Helicobacter and Related Organisms, held in Freiburg, Germany, September 1-5, 2001, are included.
pediatric disease in developing countries. The isolation and incidence rates in some developing countries have increased since their initial reports (17). 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 (26).

### Age of Infection

In developing countries, Campylobacter is the most commonly isolated bacterial pathogen from <2-year-old children with diarrhea (Table 2). 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 (Table 2), 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 (12).

### 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 (23,30). Organisms reported include Escherichia coli, Salmonella, Shigella, Giardia lamblia, and Rotavirus. Polymicrobial infections involving Campylobacter are rare in developed countries (5,6).

### Isolation of Campylobacter in Healthy Children

The recovery of Campylobacter organisms from children without diarrhea is common in developing countries. In some reports the isolation rates for symptomatic and asymptomatic children were not statistically significant. Values as high as 14.9% in controls have been observed (14). Acquisition of the pathogen because of poor sanitation and contact with animals early in life may explain the isolation from healthy children. Campylobacter is not frequently recovered from asymptomatic persons in developed countries, as observed in the Netherlands, where a 0.5% isolation rate has been reported (9).

### Seasonal Variation

In developing countries, Campylobacter enteritis has no seasonal preference; in contrast, in developed countries epidemics occur in summer and autumn (2). Isolation peaks vary from one country to another and also within countries (12,31,32). The lack of seasonal preference may be due to lack of extreme temperature variation as well as lack of adequate surveillance for epidemics (5,6).

### Distribution of Campylobacter Species

C. jejuni and C. coli are the two main species isolated in developing countries. The isolation rate of C. jejuni exceeds that of C. coli, similar to observations in most developed countries (8,9). Lior biotyping and serotyping methods have been used in developing countries to subtype strains of C. jejuni and C. coli (5,6). Table 3 shows the distribution of the subtypes from three African countries. Biotype I was the most common, followed by biotype II. The prevalence of specific serotypes only in symptomatic children may indicate virulence traits or treatment, in cases of gastroenteritis (33). Furthermore, correlation between biotypes and serotypes isolated from humans and animals indicates that campylobacteriosis is zoonotic (36). Penner serotyping scheme and DNA-based typing, extensively

<table>
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<tr>
<th>WHO region and country</th>
<th>Isolation rate (%)</th>
<th>Reference</th>
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</thead>
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<tr>
<td>Africa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Algeria</td>
<td>17.7</td>
<td>14</td>
</tr>
<tr>
<td>Cameroon</td>
<td>7.7</td>
<td>15</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>13.8</td>
<td>16</td>
</tr>
<tr>
<td>Nigeria</td>
<td>16.5</td>
<td>17</td>
</tr>
<tr>
<td>Tanzania</td>
<td>18.0</td>
<td>18</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>9.3</td>
<td>19</td>
</tr>
<tr>
<td>Americas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>9.9</td>
<td>20</td>
</tr>
<tr>
<td>Guatemala</td>
<td>12.1</td>
<td>21</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egypt</td>
<td>9.0</td>
<td>12</td>
</tr>
<tr>
<td>Jordan</td>
<td>5.5</td>
<td>22</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bangladesh</td>
<td>17.4</td>
<td>23</td>
</tr>
<tr>
<td>Thailand</td>
<td>13.0</td>
<td>24</td>
</tr>
<tr>
<td>Western Pacific</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laos</td>
<td>12.1</td>
<td>25</td>
</tr>
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WHO = World Health Organization.

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<table>
<thead>
<tr>
<th>Countries (ref.)</th>
<th>Age of infection (months)</th>
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</thead>
<tbody>
<tr>
<td>Nigeria (17)</td>
<td>24</td>
</tr>
<tr>
<td>Tanzania (18)</td>
<td>18</td>
</tr>
<tr>
<td>China (27)</td>
<td>12-24</td>
</tr>
<tr>
<td>Thailand (28)</td>
<td>&lt;12 (18.8%)</td>
</tr>
<tr>
<td></td>
<td>12-23 (12.3%)</td>
</tr>
<tr>
<td></td>
<td>24-59 (10.3%)</td>
</tr>
<tr>
<td>Bangladesh (29)</td>
<td>≤12 (38.8%)</td>
</tr>
<tr>
<td></td>
<td>&gt;12 (15.9%)</td>
</tr>
<tr>
<td>Egypt (12)</td>
<td>0-5 (8%)</td>
</tr>
<tr>
<td></td>
<td>6-11 (14%)</td>
</tr>
<tr>
<td></td>
<td>12-23 (4%)</td>
</tr>
</tbody>
</table>
used in developed countries, have been proposed for use in developing countries (37).

Species other than C. jejuni and C. coli—such as C. upsaliensis, C. concisus, and aerotolerant campylobacters (Arcobacter)—may also be of pathogenic importance; however, diagnostic capacities to determine their distribution are lacking in developing countries (38). These other Campylobacter species constitute over 50% of campylobacters isolated at the Red Cross Children’s Hospital, Cape Town, South Africa, for example. (A method termed the Cape Town Protocol is used to isolate Campylobacter species at this facility [39]). This higher incidence is also supported by a 16% isolation rate of Arcobacter species in a 4-month survey from poultry drainage water in Lagos, Nigeria (40).

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 extraintestinal infections and for treating immunocompromised persons. Erythromycin and ciprofloxacin are drugs of choice (10). 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 (41,42). For example, in 1984, 82% of Campylobacter strains from Lagos, Nigeria, were sensitive to erythromycin; 10 years later, only 20.8% were sensitive (17). In addition, resistance to another macrolide, azithromycin, was found in 7% to 15% of Campylobacter isolates in 1994 and 1995 in Thailand (43). 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 (43). Recent data have shown a marked increase in resistance to quinolones in developed countries (41,42,44-46) (Table 4).

Campylobacter as a Cause of Travelers’ 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 (47,48). Furthermore, campylobacteriosis acquired abroad contributes to the number of cases reported in developed countries (49). Among Finnish tourists visiting Morocco, the disease was more prevalent in winter months (50).

Clinical Features

The clinical spectrum of Campylobacter enteritis ranges from a watery, nonbloody, noninflammatory 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).

Guillain-Barré Syndrome

Guillain-Barré Syndrome (GBS) is an autoimmune disorder of the peripheral nervous system, which is characterized by acute flaccid paralysis. C. jejuni infection is the most frequently identified infection preceding GBS (52). In the developing world, sporadic GBS cases associated with C. jejuni infection have been reported from Curaçao, China, India, and South Africa (26,53-55). A comparative study between Curaçao and southwest Netherlands indicated that disease in Curaçao was more severe, had a higher incidence of preceding gastroenteritis, and had greater seasonal fluctuation (26). Serotype O:19 is most prevalent worldwide, although other serotypes, such as O:1, O:2, O:57, O:16, O:23, O:37, O:41, and

Table 3. Distribution of Campylobacter jejuni and C. coli biotypes and serotypes in three African countries

<table>
<thead>
<tr>
<th>Countries (ref.)</th>
<th>Biotypes</th>
<th>Serotypes</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>C. jejuni</td>
<td>C. coli</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Nigeria (33)</td>
<td>52.5</td>
<td>28.7</td>
</tr>
<tr>
<td>Central African Republic (34)</td>
<td>31.9</td>
<td>11.0</td>
</tr>
<tr>
<td>South Africa (35)</td>
<td>95.4</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Table 4. Trends in Resistance to Ciprofloxacin by Campylobacter jejuni in selected developed countries up to year 2000

<table>
<thead>
<tr>
<th>Country</th>
<th>Period</th>
<th>Resistance strains (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freiburg, Germany</td>
<td>1992-2000</td>
<td>22 (32)</td>
</tr>
<tr>
<td>Styria, Austria</td>
<td>1996-2000</td>
<td>40 (25.2)</td>
</tr>
<tr>
<td>England and Wales, UK</td>
<td>1993-2000</td>
<td>10 (14.8)</td>
</tr>
<tr>
<td>Philadelphia, USA</td>
<td>1995-2000</td>
<td>&lt;10 (36)</td>
</tr>
<tr>
<td>Oslo, Norway</td>
<td>1988-2000</td>
<td>6.1 (36)</td>
</tr>
</tbody>
</table>

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SYNOPSIS

Campylobacter Infection in the Setting of HIV

Campylobacter-associated diarrhea and bacteremia occur in HIV/AIDS patients worldwide. The species isolated include C. jejuni, C. coli, C. upsaliensis, Arcobacter butzleri, Helicobacter fennelliae, and H. cinaedi (57,58). 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 (59). 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 (60). 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.

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 (61-64). 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 (65). 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 (63). 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 (28,66).

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 (67). In Algeria, exclusively breast-fed infants had fewer symptomatic Campylobacter infections than infants who were both breast-fed and bottle-fed (14).

Results of experimental observations among Mexican children have also shown that immunity to Campylobacter after primary infection may prevent bloody diarrhea from developing and subsequently prevent any disease from manifesting (68). 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) (28). The widespread immunity seen among adults in developing countries is absent in adults in developed countries (64).

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 (5,12), although observations from developed countries show these are less likely factors (2).

Environmental Contamination

Wild birds as well as domestic and companion animals are known reservoirs for Campylobacter species, and shedding of the bacteria from them causes contamination of the environment. C. jejuni and C. coli have been isolated from chickens, goats, sheep, and pigs in developing countries (69,70). Strains isolated from human and chickens were phenotypically and genotypically correlated, confirming that chickens are an important source of human campylobacteriosis in developing countries (36). Poultry is also an important source of campylobacteriosis in developed countries. Extensive epidemiologic investigations have been done in those countries to identify sources of contamination and routes of transmission to humans to facilitate control efforts (71). Risk factors for acquiring campylobacters in developing countries include presence of an animal in the cooking area, uncovered garbage in cooking areas, and lack of piped water (12).

Foods

Campylobacter-contaminated foods—the result of poor sanitation—are an important potential source of infection in humans. For example, campylobacters were isolated from 40% and 77% of retail poultry meat sold in Bangkok, Thailand, and Nairobi, Kenya, respectively (72,73). The serotypes of the organisms isolated in Thailand were similar to those of organisms isolated from humans. In Mexico City, a survey of ready-to-eat roasted chickens showed that they were
contaminated with campylobacters (74). 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 (2).

**Estimates of Impact of Human Campylobacteriosis in Developing Countries**

The Disability Adjusted Life Year (DALY) is the basic unit used in Burden of Disease (BoD) methodology to quantify the impact of disease on a population (75). DALYs have been applied in the Dutch population to measure the mean health burden of Campylobacter-associated illness in the period 1990–1995 (76). The mean estimate was 1,400 DALYs per year; the main determinants of health burden were acute gastroenteritis (440 DALYs), gastroenteritis-related mortality (310 DALYs), and residual symptoms of GBS (340 DALYs).

Although data on DALYs due to campylobacteriosis in developing countries are not available, diarrhea, which is a clinical manifestation of campylobacteriosis, was one of the top three causes of death and disease in developing countries in 1990 (75). The disease is projected globally to remain one of the top 10 by 2020. (The burden of campylobacteriosis in developing countries may increase by 2020 because HIV is projected to move up to the 10th position from 28th by 2020.) Considering the higher incidence of campylobacteriosis in developing countries, DALYs for the disease in developing countries will likely be higher than those of the Dutch population.

**Conclusions**

The incidence of human campylobacteriosis is increasing worldwide and has attracted the attention of WHO (http://www1.oecd.org/agr/prog/sum-copenhagen00.htm). Substantial gaps in knowledge about the epidemiology of campylobacteriosis in developing countries still exist. Present reported estimates of incidence are based on isolation rates from laboratory- and community-based studies conducted from 1980 to 1995. 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, and the role of campylobacteriosis in GBS. Collaboration among researchers in developed and developing countries needs to be strengthened, leading to development of regional centers of excellence. Funding organizations should provide incentives for North-South collaborations in Campylobacter research, as is done in other diseases such as malaria and trypanosomiasis that are endemic in some developing countries. All these should contribute to understanding of the global epidemiology of human campylobacteriosis.

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Akitoye O. Coker is a Consultant Microbiologist and Professor of Medical Microbiology at the University of Lagos, Nigeria. He pioneered research into Campylobacter enteritis in Lagos, Nigeria.

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