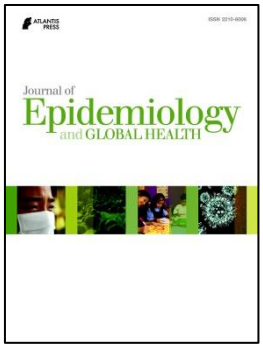

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Burden of laboratory-confirmed *Campylobacter* infections in Guatemala 2008—2012: Results from a facility-based surveillance system

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Abstract *Introduction:* Campylobacteriosis is one of the leading causes of gastroenteritis worldwide. This study describes the epidemiology of laboratory-confirmed *Campylobacter* diarrheal infections in two facility-based surveillance sites in Guatemala.

Methods: Clinical, epidemiologic, and laboratory data were collected on patients presenting with acute diarrhea from select healthcare facilities in the departments of Santa Rosa and Quetzaltenango, Guatemala, from January 2008 through August 2012. Stool specimens were cultured for *Campylobacter* and antimicrobial susceptibility testing was performed on a subset of isolates. Multidrug resistance (MDR) was defined as resistance to $\geqslant 3$ antimicrobial classes.

Results: *Campylobacter* was isolated from 306 (6.0%) of 5137 stool specimens collected. For children <5 years of age, annual incidence was as high as 1288.8 per 100,000 children in Santa Rosa and 185.5 per 100,000 children in Quetzaltenango.

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Among 224 ambulatory care patients with *Campylobacter*, 169 (75.5%) received metronidazole or trimethoprim-sulfamethoxazole, and 152 (66.7%) received or were prescribed oral rehydration therapy. Antimicrobial susceptibilities were tested in 96 isolates; 57 (59.4%) were resistant to ciprofloxacin and 12 (12.5%) were MDR.

Conclusion: Campylobacter was a major cause of diarrhea in children in two departments in Guatemala; antimicrobial resistance was high, and treatment regimens in the ambulatory setting which included metronidazole and trimethoprim-sulfamethoxazole and lacked oral rehydration were sub-optimal.

1. Introduction

Campylobacteriosis, usually acquired by the consumption and handling of poultry — is one of the leading causes of gastroenteritis worldwide [1]. The illness is characterized by diarrhea, abdominal cramps, and fever [2]. Although mortality is rare, significant post-infectious sequelae such as Guillain—Barré syndrome, irritable bowel syndrome, and reactive arthritis do occur [3—6]. The utilization of fluoroquinolones in feed animals to treat illness and promote growth has contributed to increasingly quinolone-resistant *Campylobacter* strains [7,8], complicating the treatment for patients with severe disease and immunocompromised states, especially children [1].

In Guatemala, diarrhea is the second most common cause of morbidity and mortality in children <5 years of age [9]. Small, community-based studies in Guatemala suggest that *Campylobacter* is a common cause of diarrhea in children [10,11]. However, no estimates have been generated for the incidence of campylobacteriosis in Guatemala or for the degree of antimicrobial resistance. Identification of *Campylobacter* requires specific culturing techniques with micro-aerobic environments [12], and few laboratories in Guatemala routinely culture for this pathogen.

In this report, cases are characterized and the incidence of laboratory-confirmed campylobacteriosis is estimated from a facility-based surveillance system in Guatemala from 2008 through 2012.

2. Methods

2.1. Study sites

In July 2007, the U.S. Centers for Disease Control and Prevention's (CDC) International Emerging Infections Program (IEIP) in Guatemala, in collaboration with the Ministry of Public Health and Welfare (MSPAS) and the Universidad del Valle de Guatemala (UVG), initiated a facility-based surveillance system in the department of Santa Rosa. Additional sites in the department of Quetzaltenango were added in February of 2009. The surveillance system captures patients of all ages in both ambulatory and hospital settings, and diarrhea is one of the syndromes under surveillance.

Santa Rosa, with a population of 346,590 persons, is one of 22 administrative departments in Guatemala, and it is located in the semi-tropical southern part of the country. Ethnically, the population is 15% Amerindian indigenous [13]. Quetzaltenango, with a population of 789,358 persons, is in the western highlands and has a population that is 62% Amerindian indigenous. Government health facilities include hospitals, health centers staffed by a physician and nurses, and health posts staffed by nurses. In both surveillance sites, the facility-based system includes a hospital and an ambulatory component. In Santa Rosa, the surveillance system includes the regional hospital in Cuilapa, the municipal capital of Santa Rosa, as well as the health center and five health posts of the municipality of Nueva Santa Rosa, located 30 km north of Cuilapa. In Quetzaltenango, surveillance includes the regional hospital in the capital of Quetzaltenango, as well as the three health centers and one health post in the municipalities around the capital. In this analysis, the health centers and health posts were collectively considered ambulatory care facilities, and cases captured in these facilities were used for ambulatory surveillance. Data were included from Santa Rosa between January 2008 and August 2012, and from Quetzaltenango between February 2009 and August 2012.

2.2. Case detection and data collection

A case of diarrhea was defined as $\geqslant 3$ loose or liquid stools in a 24-h period with onset within the seven days preceding presentation to any participating facility by a patient residing in a municipality covered by the surveillance system. To avoid enrolling patients with chronic diarrhea, subjects were excluded if they had any signs or symptoms of diarrhea within the seven days prior to the onset of the current illness. Surveillance nurses screened patients by reviewing log book entries and

assessing chief complaints for diarrhea-related visits and admissions. These patients were interviewed, and if found to meet the case definition, detailed clinical, epidemiologic, demographic, and socioeconomic data were obtained through structured patient interviews and medical chart abstractions [14]. In the ambulatory setting, facilities were staffed with surveillance nurses during all working hours and all patients presenting with diarrhea were screened for eligibility. In the hospital setting, except for holidays, surveillance nurses were on-duty seven days per week from 8:00 AM to 5:00 PM. Only patients who were admitted to the hospital were screened for eligibility. This insured that only severe cases of diarrhea were enrolled in hospital surveillance, and it also was the only feasible approach since surveillance nurses were not able to collect all the necessary laboratory and epidemiologic data from patients in the emergency department (ED) before they were discharged.

2.3. Laboratory methods

A stool specimen was requested of all consenting patients. For children <5 years of age who were unable to produce a specimen, a rectal swab was collected and placed in Cary-Blair transport media. Stool samples from the ambulatory facilities were stored in Cary-Blair transport media in an insulated cooler at 4 °C, and transported within 24 h to one of the two regional hospitals for initial processing and testing. Samples were streaked by direct plating onto *Campylobacter* selective agar base, Karmali (Oxoid, Basingstoke, UK) and incubated at 42 °C for 48 h under microaerophilic conditions provided by the CampyGen™ Generating System (Oxoid, Basingstoke, UK). Small, gray, moist, and flat spreading colonies were considered suspicious of *Campylobacter*, and were placed on a stained slide for microscopic examination. On visual examination, colonies with ''gull-winged,'' spiral, or ''S''-shaped structures were considered microscopically suspect colonies, and were subsequently plated on Mueller Hinton (Oxoid, Basingstoke, UK) or blood agar and tested with oxidase and catalase and the Dryspot *Campylobacter* test kit (Oxoid, Basingstoke, UK) to confirm *Campylobacter*. The hippurate test was used to identify *C. jejuni* [15]. A specimen was considered negative for *Campylobacter* if no suspicious colonies grew after 72 h of incubation. Isolates were sent to UVG laboratories for *Campylobacter* and *C. jejuni* confirmation and antimicrobial susceptibility testing. Due to limited supplies, antimicrobial susceptibility testing was performed on all cultures done from 2010 to 2011 that grew *Campylobacter*, using minimum inhibitory concentrations (MIC) via Etest® (Biomérieux, Marcy l'Etoile, France) for the following antimicrobial agents: nalidixic acid (NA), chloramphenicol, ciprofloxacin, erythromycin, and tetracycline [16]. Multidrug-resistance (MDR) was defined as resistance to at least one antimicrobial in at least three of the following antimicrobial groups: macrolides, quinolones, phenicol, and tetracycline [17,18].

2.4. Data analysis

The number of laboratory-confirmed *Campylobacter* infections was examined by quarter and stratified by ambulatory and hospital settings separately for Santa Rosa and Quetzaltenango. The total number of diarrhea cases that were captured by the surveillance system was also displayed per quarter. Seasonality of *Campylobacter* infections was assessed visually using time series graphs.

Annual crude rates for *Campylobacter* were calculated. Population denominators were obtained for the catchment area of the surveillance facilities by healthcare setting for all ages and for children <5 years, from 2000 through 2010 municipality data from Guatemala's National Institute of Statistics (INE) [13]. Population estimates for the catchment areas in 2011 and 2012 were generated by calculating the average change in municipality population by age from 2009 to 2010, then assuming that same change for 2011 and 2012.

Demographic and clinical characteristics of case—patients treated at ambulatory and hospital settings were compared using chi square tests. Fisher's exact tests were used when cell sizes had counts of five or less. Demographic, geographic, healthcare setting, and clinical differences were explored between patients who had antimicrobial susceptibility data versus those who did not using chi square tests. The proportion resistant was calculated for each of the five tested antimicrobials for all *Campylobacter* and the subset of *C. jejuni*. In addition, the difference was tested in the proportion of isolates that were MDR from ambulatory versus hospital settings using Fisher's exact test.

2.5. Ethics

The surveillance protocol was approved by the institutional review boards of the CDC and the UVG, and approved by the Guatemalan MSPAS. Verbal consent was requested of patients in order to screen them for eligibility. Written, informed consent was obtained from eligible patients who were willing to participate. For patients <18 years of

Table 1 Number and crude rates of laboratory-confirmed *Campylobacter* cases captured at Santa Rosa and Quetzaltenango[a] surveillance sites by healthcare setting, January 1, 2008 – August 31, 2012.

	Santa Rosa				Quetzaltenango			
	Hospital		Ambulatory		Hospital		Ambulatory	
	Number of cases	Crude rate per 100,000 persons	Number of cases	Crude rate per 100,000 persons	Number of cases	Crude rate per 100,000 persons	Number of cases	Crude rate per 100,000 persons
2008								
<5 years	3	8.1	27	594.5	n/a	n/a	n/a	n/a
All	3	1.2	28	92.5				
2009								
<5 years	6	16.1	34	745.5	n/a	n/a	n/a	n/a
All	6	2.4	39	127.3				
2010								
<5 years	17	45.0	59	1288.8	3	5.4	6	48.3
All	17	6.6	67	215.8	3	0.8	7	8.5
2011								
<5 years	0	0	46	1001.1	3	5.3	7	55.2
All	0	0	47	149.5	4	1.1	8	9.4
2012[b]								
<5 years	4	25.0	28	910.7	5	13.2	16	185.5
All	4	4.1	32	150.8	5	1.9	16	27.3

[a] Surveillance in Quetzaltenango began in 2009.
[b] Rates account for partial year through August 31.

age, parents or guardians were asked to provide written, informed consent for the participation of the patient. In addition, children aged 7 through 17 were asked for written, informed assent.

3. Results

During the five-year analysis period in Santa Rosa, 4327 patients met the case definition for diarrhea and all but one consented to participate; 246 (6.3%) of 3929 (90.8%) stool specimens collected yielded cultures positive for *Campylobacter*. During the three-year analysis period in Quetzaltenango, 1336 patients met the case definition for diarrhea and all but one consented to participate; 60 (5.0%) of 1208 (90.4%) stool specimens collected yielded cultures positive for *Campylobacter*. No seasonal pattern of disease was evident by visual inspection of time series graphs. In the hospital setting in Santa Rosa during 2008 through 2012, the median crude annual incidence of *Campylobacter* infections was 2.4 per 100,000 persons (range, 0–6.6) for all ages, and 16.1 per 100,000 persons (range, 0–45.0) for children <5 years old (Table 1). Median incidence in the ambulatory setting in Santa Rosa was 149.5 per 100,000 persons (range, 92.5–215.8) for all ages, and 910.7 per 100,000 persons (range, 594.5–1288.8) for children <5 years old. In the ambulatory setting in Quetzaltenango during 2010 through 2012, the median crude annual rate was 9.4 per 100,000 persons (range, 8.5–27.3) for all ages, and 55.2 per 100,000 persons (range, 48.3–185.5) for children <5 years old. Of the 306 *Campylobacter* cases, 235 (76.8%) were *C. jejuni* (Table 2).

During the study period, the number of laboratory-confirmed *Campylobacter* infections and diarrhea cases captured by the surveillance system per quarter varied, especially for Santa Rosa (Fig. 1a and b). In Santa Rosa, the median proportion of cases with a confirmed *Campylobacter* infection per stool culture performed per quarter was 8.0% (range, 0.4–17.1%) in the ambulatory setting and 4.1% (range, 0–11.1%) in the hospital setting. In Quetzaltenango, the median proportion was 3.9% (range, 0–13.5%) in the ambulatory setting and 5.0% (range, 0–15.8%) in the hospital setting. The proportion of cases presenting to ambulatory versus hospital settings was higher for both Santa Rosa (86.6%) and Quetzaltenango (73.3%).

Over 40% of the *Campylobacter* infections occurred in children <1 year of age, over 90% in children <5 years (<50% of patients screened were <5 years of age) (Table 2). More patients presenting to the ambulatory versus hospital settings stated that they had abdominal pain or cramping ($p = 0.0002$). Over 40% of hospitalized versus 17.0% of ambulatory case–patients had an axillary temperature of $\geqslant 38$ °C ($p = 0.0002$). A higher proportion of hospitalized case–patients showed signs