Trends of Norfloxacin and Erythromycin Resistance of *Campylobacter jejuni/Campylobacter coli* Isolates Recovered From International Travelers, 1994 to 2006

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Background. *Campylobacter* sp. is a major cause of bacterial enterocolitis and travelers' diarrhea. Empiric treatment regimens include fluoroquinolones and macrolides.

Methods. Over the period 1994 to 2006, 724 *Campylobacter jejuni/Campylobacter coli* isolates recovered from international travelers at the outpatient clinic of the Institute of Tropical Medicine, Antwerp, Belgium, were reviewed for their susceptibility to norfloxacin and erythromycin.

Results. Norfloxacin resistance increased significantly over time in isolates from travelers returning from Asia, Africa, and Latin America. For the years 2001 to 2006, norfloxacin resistance rates were 67 (70.5%) of 95 for Asia, 20 (60.6%) of 33 for Latin America, and 36 (30.6%) of 114 for Africa. The sharpest increase was noted for India, with no resistance in 1994, but 41 (78.8%) of 52 resistant isolates found during 2001 to 2006. Erythromycin resistance was demonstrated in 20 (2.7%) isolates, with a mean annual resistance of 3.1% ± 2.8%; resistance increased over time, with up to 3(7.5%) of 40 and 3 (8.6%) of 35 resistant isolates in 2004 and 2006, respectively ($p < 0.05$); there was no apparent geographic association. Combined resistance to norfloxacin and erythromycin was observed in five isolates.

Conclusions. The high resistance rates to fluoroquinolones warrant reconsideration of their use as drugs of choice in patients with severe gastroenteritis when *Campylobacter* is the presumed cause. Continued monitoring of the incidence and the spread of resistant *Campylobacter* isolates is warranted.

The genus *Campylobacter* is considered a major cause of human bacterial enterocolitis worldwide and is responsible for 400 to 500 million cases of diarrhea each year.[1] *Campylobacter jejuni* represents the most frequently involved species. In developed countries, foreign travel is a main risk factor for contracting *Campylobacter* enteritis,[2] and in some countries, the numbers of *Campylobacter* infections contracted abroad outnumber those acquired domestically.[3,4] In developing countries, *Campylobacter* enteritis affects mainly children younger than 5 years.[5] Transmission of *Campylobacter* occurs through handling and consumption of poultry meat in industrialized countries, and by water and contact with farm animals in developing countries.[5]

If antibiotic therapy for travelers' diarrhea is indicated, the empiric use of a fluoroquinolone or a macrolide antibiotic is advised. The latter choice is preferred when the likelihood of *Campylobacter* spp. being the etiologic agent is high and for confirmed cases of *Campylobacter* enteritis requiring treatment.[6] Fluoroquinolone resistance in *Campylobacter* spp. has increased since the 1990s.[7–10] In addition, *Campylobacter* isolates with macrolide resistance or fluoroquinolone–macrolide coresistance are reported.[7,8,10,11] Although resistant strains are described in several parts of the world, large geographical differences occur, and in many regions, resistance levels remain low.[9–12]

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The aim of this study was to review trends and evolution of fluoroquinolone and macrolide resistance in *Campylobacter* isolates recovered from international travelers.

Materials and Methods

In this retrospective study, consecutive *Campylobacter* isolates recovered during the period 1994 to 2006 were included. They were cultured from patients attending the outpatient travel clinic of the Institute of Tropical Medicine (ITM), Antwerp, Belgium. Stool samples were submitted on clinical indication. For each patient, the country of travel destination was recorded. Isolates recovered from patients without travel history were included as domestic controls; most of these patients were attending the outpatient clinic of sexually transmitted infections and infections due to human immunodeficiency virus at ITM.

Stool samples were inoculated on Campylosel Agar (bioMérieux, Marcy-L'étoile, France) and incubated in a microaerobic atmosphere (generated by Anaerocult C, Merck, Darmstadt, Germany) at 42°C for 48 hours. The isolates were identified by standard microbiologic methods including colonial morphology, Gram stain, catalase and oxidase reactions, and hydrolysis of hippurate and indoxyl acetate.

As part of the diagnostic laboratory workup, susceptibilities to norfloxacin (fluoroquinolone) and erythromycin (macrolide) were determined by disk diffusion. A 1.0 McFarland suspension was made from an overnight culture and inoculated on Mueller–Hinton agar supplemented with 5% defibrinated sheep blood (bioMérieux). Disks (Rosco, Taastrup, Denmark) with erythromycin (78 μg) and norfloxacin (10 μg) were added and plates incubated at 42°C in a microaerobic atmosphere for 24 hours. Inhibition diameters were measured and interpreted according to the instructions of the manufacturer. Breakpoint susceptibility and resistance points were ≤1 and >4 mg/L for erythromycin, and ≤0.5 and >1 mg/L for norfloxacin, respectively.

For each patient, only the first isolate was considered, unless successive isolates were contracted at different episodes and different travel destinations. For comparison, destinations were grouped according to continents and travel regions.[4] Norfloxacin resistance rates for the period 2001 to 2006 were compared to those for the period 1994 to 2000 and tested for significance using the chi-square test. Evolutions of resistance over the years for norfloxacin and erythromycin were assessed for significance using the score test for trend of odds. All analyses were performed using Stata software (version 8.2; Stata Corp, College Station, TX, USA).

Results

Inclusion of Isolates

Among 26,450 samples submitted, 786 consecutive *Campylobacter* isolates were recovered (isolation rate 3.0%). Two isolates did not grow on susceptibility testing, and from 41 isolates, no information on travel history was available. Further, a total of 19 isolates were considered as repeat isolates, leaving 724 isolates recovered in 722 patients for analysis (two patients contracted successive *Campylobacter* infections at different travel destinations). The vast majority of isolates (722, 99.7%) were identified as *C jejuni*, and the remaining two as *C coli*.

Isolates were most often recovered from patients returning from Asia ($n = 303$), Africa ($n = 276$), and the Caribbean and Central and South America (Latin America, $n = 69$). Other travel destinations included Europe ($n = 31$) and Australia ($n = 1$). A total of 44 isolates were domestic isolates. Countries with high numbers of isolates included India ($n = 169$), Thailand ($n = 35$), and the Democratic Republic of the Congo ($n = 37$).

Norfloxacin Resistance

A total of 254 (35.1%) isolates (including the two *C coli* isolates) were norfloxacin resistant. Table 1 lists the numbers of isolates recovered from travelers according to travel destination. For the years 2001 to 2006, norfloxacin resistance rates were 67(70.5%) of 95 for Asia, 20 (60.6%) of 33 for Latin America, and 36 (30.6%) of 114 for Africa (mainly North and Central Africa). Domestic isolates also showed a significant increase in resistance between the two periods. Figure 1 illustrates the annual trends in norfloxacin resistance for Asia, Africa, and the other travel destinations (Latin America and Europe, except domestic isolates) combined; all three reached significance ($p < 0.001$). Asia showed the most pronounced increase in resistance. In particular, India showed a sharp and significant ($p < 0.001$) increase in resistance over time: in 1994, no resistance was noted, but in the period 2001 to 2006, resistance was demonstrated in 41(78.8%) of 52 isolates.

Erythromycin Resistance

Erythromycin resistance was demonstrated in 20 (2.7%) isolates (all identified as *C jejuni*). Mean annual resistance rate was 3.1% ± 2.8%. Resistance significantly increased over time, with up to 3

Table 1 *Campylobacter* isolates recovered from international travelers: regions of travel destination matched with norfloxacin resistance

Region	Period 1994–2000			Period 2001–2006			*p* Values
	Total number of isolates	No. resistant isolates	Resistance rate (%)	Total number of isolates	No. resistant isolates	Resistance rate (%)	
North Africa	11	3		14	7		
East Africa	54	8		41	9		
West Africa	42	3	7.1	28	8	28.6	$p < 0.05$
Southern Africa	14	0		8	3		
Central Africa	41	8		23	9		
Africa in total	162	22	13.6	114	36	31.6	$p < 0.001$
East Asia	65	31	47.7	43	26	60.5	
Indian subcontinent	138	40	29.0	52	41	78.8	$p < 0.001$
Arab countries and Iran	5	3		0	0		
Asia in total	208	74	35.6	95	67	70.5	$p < 0.001$
Caribbean and Central and South America	36	10	27.8	33	20	60.6	$p < 0.05$
Other	19	4	21.1	13	10	76.9	$p < 0.05$
Domestic	23	2	8.7	21	9	42.9	$p < 0.05$

North Africa: Egypt (*n* = 9), Morocco (*n* = 13), Tunisia (*n* = 3).
East Africa: Burundi (*n* = 9), Ethiopia (*n* = 23), Kenya (*n* = 16), Niger (*n* = 12), Rwanda (*n* = 15), Somalia (*n* = 1), Sudan (*n* = 3), Uganda (*n* = 4), Tanzania (*n* = 12).
West Africa: Benin (*n* = 4), Burkina Faso (*n* = 15), Cape Verde (*n* = 1), Côte d'Ivoire (*n* = 11), Gambia (*n* = 1), Ghana (*n* = 5), Mali (*n* = 10), Mauritania (*n* = 1), Senegal (*n* = 17), Sierra Leone (*n* = 1), Togo (*n* = 4).
Southern Africa: Angola (*n* = 6), Botswana (*n* = 1), Madagascar (*n* = 4), Mozambique (*n* = 1), South Africa (*n* = 3), Zambia (*n* = 6), Zimbabwe (*n* = 1).
Central Africa: Cameroon (*n* = 5), Central African Republic (*n* = 3), Chad (*n* = 8), Congo (*n* = 1), Democratic Republic of the Congo (*n* = 37), Gabon (*n* = 1), Guinea (*n* = 4), Nigeria (*n* = 5).
East Asia: Cambodia (*n* = 7), China (*n* = 12), Democratic Republic of Korea (*n* = 1), Indonesia (*n* = 28), Japan (*n* = 1), Lao People's Democratic Republic (*n* = 3), Malaysia (*n* = 3), Mongolia (*n* = 1), Myanmar (*n* = 3), Philippines (*n* = 4), Republic of Korea (*n* = 1), Thailand (*n* = 38), Singapore (*n* = 1), Timor-Leste (*n* = 1), Viet Nam (*n* = 7).
Indian subcontinent: Bangladesh (*n* = 3), Bhutan (*n* = 1), India (*n* = 169), Nepal (*n* = 5), Pakistan (*n* = 5), Sri Lanka (*n* = 7).
Arab countries and Iran: Islamic Republic of Iran (*n* = 1), Lebanon (*n* = 1), Syrian Arab Republic (*n* = 2), Yemen (*n* = 1).
Caribbean and Central and South America: Cuba (*n* = 2), Dominican Republic (*n* = 4), Haiti (*n* = 28), Jamaica (*n* = 1), Costa Rica (*n* = 1), Guadeloupe (*n* = 1), Guatemala (*n* = 4), Mexico (*n* = 4), Argentina (*n* = 1), Bolivia (*n* = 1), Brazil (*n* = 6), Colombia (*n* = 1), Ecuador (*n* = 1), Guyana (*n* = 1), Honduras (*n* = 1), Paraguay (*n* = 1), Peru (*n* = 8), Venezuela (*n* = 1).
Other: Romania (*n* = 2), Greece (*n* = 2), Israel (*n* = 1), Turkey (*n* = 12), Sweden (*n* = 1), Russian Federation (*n* = 1), Italy (*n* = 4), Portugal (*n* = 1), Spain (*n* = 4), France (*n* = 3), Australia (*n* = 1).

(7.5%) of 40 and 3 (8.6%) of 32 isolates in 2004 and 2006, respectively ($p < 0.05$). India and Haiti accounted for five erythromycin-resistant isolates each, but overall, erythromycin resistance was not confined to any particular region. Coresistance to norfloxacin and erythromycin was observed in five isolates (acquired in Lebanon, Thailand, Spain, Egypt, and India).

Discussion

In this study, we demonstrated among international travelers a significant increase of norfloxacin resistance in *C jejuni/coli* isolates during the past 13 years. During the years 2000 to 2006, resistance to this drug was observed in more than 60% of isolates recovered from travelers returning from Asia, Latin America, and Europe outside Belgium, and in more than 30% in those returning from Africa. Macrolide resistance increased significantly over time (up to 8.6% in 2006) but showed no clear geographic association.

Limitations of the Study

Several factors should be considered when comparing results of *Campylobacter* susceptibility studies. The agar dilution method has recently been proposed as the reference method, but because of its labor intensity and cost, this method is less feasible in the routine diagnostic setting, where disk diffusion methods or the E-test is preferred.[13–18] The presently used disk diffusion method has proved to be reliable in the setting of single laboratories, and disk diffusion tests generate a classification into susceptible and resistant isolates, which is in accordance with the reference method.[19–21] With regard to the choice of antimicrobials, it should be noted that there is complete cross-resistance between erythromycin and the newer macrolides,[20] and susceptibilities and resistances for norfloxacin completely

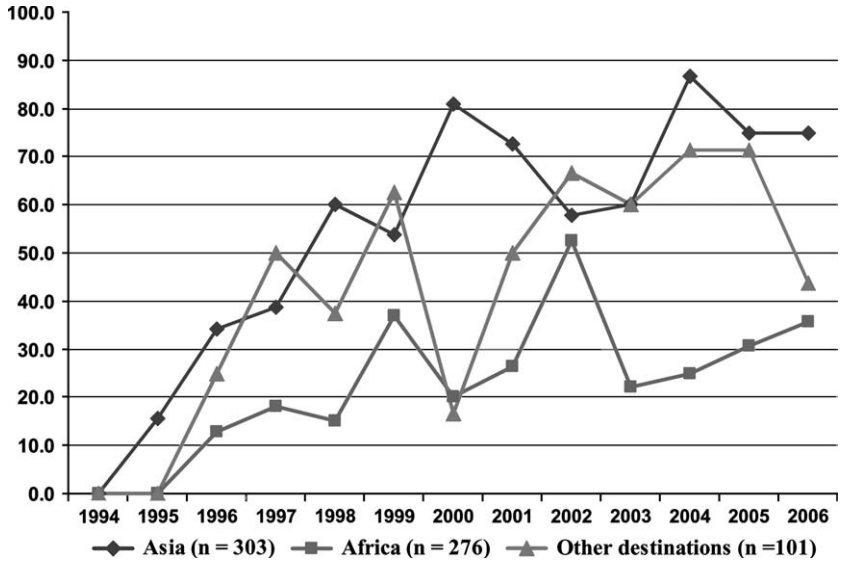

Figure 1 Annual rates of norfloxacin resistance in *Campylobacter* isolates recovered from travelers on their return from Asia, Africa, and other travel destinations (the Caribbean, Central and South America, Europe without Belgium and Australia) combined, $p < 0.001$ for the three groups.

match those for ciprofloxacin, which is the benchmarking antibiotic in other studies.[10,15,19,22,23]

In addition to these technical limitations, the clinical setting and sample strategy are also of importance. For instance, we studied consecutive isolates mainly from adult outpatients, while others focused on hospitalized patients, children, or military personnel, or even included clustered isolates recovered from outbreaks.[14,19,24–26] Further, the retrospective nature of this study did not allow tracing previous therapy as a cause of fluoroquinolone resistance. Fluoroquinolone resistance can emerge during therapy, but this accounts only for a small part of acquired resistance (15% in the study of Smith and colleagues[2]), and for the present study, we assume this factor to have been constant over time and regions.

Comparison With Other Findings

The emergence of resistance among *Campylobacter* spp. during the 1990s is reviewed by Engberg and colleagues.[9] Highest fluoroquinolone resistance rates (>70%) are repeatedly reported from Spain and Thailand[8–10,24] and have recently been described in the Arab Emirates and Hong Kong.[14,27] Our study confirms the high resistance rates in these parts of the world. In addition, it provides statistical evidence as to the increase of resistance in Latin America and the Indian subcontinent, and it adds data on the rising resistance rates in Africa.

Unlike Thailand, *Campylobacter* susceptibility patterns in India and other Asian countries are scarcely documented. In 1994, a low frequency of fluoroquinolone resistance was reported in India (4.4% of human isolates).[28] A recent study of human isolates in a rural population in northern India demonstrated an elevated resistance rate (71.4%), but contrasts to another study reporting no resistance among animal and environmental strains.[29]

The situations for Africa and the Americas are less studied. Although sample sizes of earlier studies were insufficient for determining significance, Finish and Spanish travelers on their return from Africa showed resistance rates of 38.0% and 37.5%, which are similar to those found in the present study.[10,18] In addition, both studies revealed a tendency to increased resistance. Two recent studies from Africa confirmed these resistance rates: a study in Egyptian children revealed an increasing fluoroquinolone resistance over the years 1995 to 2000,[26] and another study from Senegal found a 34% resistance rate among isolates recovered from chicken carcasses.[30] For Central and South America, the Spanish study cited above reported a 45.4% resistance rate on a limited number of patients, while the Finish study included too few numbers for analysis.[10,18] A single study from Chile over the years in 2000 reported no fluoroquinolone resistance among pediatric isolates recovered during 1996 to 1997.[31]

Although it was not the primary purpose of our study, we also demonstrated an increase in fluoroquinolone resistance among domestic isolates. The domestic resistance rates for the period 2001 to

2006 (42.9%) matches those reported among poultry isolated in Belgium[32] and among human isolated in other European countries.[25,33]

Our study also showed increasing macrolide resistance, although they remained low. Macrolide resistance in *Campylobacter* differs by country and species.[34] It predominates among *C coli* (with up to two thirds of isolates resistant) but rarely exceeds 10% in *C jejuni*.[9,11] In Western countries, trends over time are stable.[9,34] The highest macrolide resistance rates (31%) were reported 10 years ago from Thailand[7] and Nigeria.[35] Earlier studies on travelers in Western countries did not report increasing macrolide resistance, which may be partly explained by the lower numbers included.[16,18] In line with our findings, however, are those reported among Egyptian children, revealing a trend of increasing resistance over time for erythromycin.[26]

Both macrolide and fluoroquinolone resistance are reported to be associated with coresistance (resistance to both first-line drugs) and multidrug resistance (resistance to additional antibiotics such as tetracyclines, gentamicin, and cefotaxime). Coresistance and multiresistance have been reported from different parts of the world, especially from Asia.[8,11,29] Although coresistant isolates were not frequent in the present study, it is clear that emergent erythromycin resistance is a major public health concern and calls for continuous monitoring of resistance in *Campylobacter* isolates.[34]

Mechanisms of Resistance and Factors Influencing Emergence and Spread of Resistance

The *Campylobacter* species are naturally susceptible to fluoroquinolones and macrolides.[9] Fluoroquinolone resistance in *C jejuni* is most often due to single point mutation in the genes encoding subunits of DNA gyrase (*gyr*A) and occasionally of topoisomerase IV subunit *par*C. In Western countries, most investigators conclude that fluoroquinolone resistance in *C jejuni* and *C coli* is driven by veterinary use of antibiotics, especially in poultry. Both European countries and the United States witnessed a dramatic increase in fluoroquinolone resistance of *Campylobacter* spp. in a timely relation to the use of fluoroquinolone antibiotics in veterinary medicine.[9,15,36] By contrast, in Australia, where fluoroquinolones are not approved for use in food-producing animals, and where only cooked chicken products can be imported, ciprofloxacin resistance remains limited to 2%.[12]

Resistance to macrolides is caused by point mutations in the peptidyl-encoding region in the domain V of the 23S ribosomal RNA gene, thereby modifying the target ribosomal proteins.[9,34] Macrolide resistance is most prevalent among *Campylobacter* isolates recovered in animals and has been related to their use as growth promoters, especially in pigs.[34] In addition, macrolide resistance may develop in areas with a large reservoir of human asymptomatic *Campylobacter* carriers (such as developing countries[5]) and frequent use of macrolides in humans.[9]

Clinical Relevance of Fluoroquinolone Resistance

Campylobacter enterocolitis is generally self-limited, and antibiotic therapy is not required unless in immunosuppressed individuals and in cases of relapsing or unremitting inflammatory diarrhea.[36] Erythromycin is the drug of choice. Newer macrolides such as azithromycin offer improved pharmacokinetics and dosing and have activity against other bacteriologic causes of diarrhea. Fluoroquinolones, by virtue of their broad activity against enteropathogens, are alternatives and recommended as empirical treatment for travelers' diarrhea.[37]

Observational studies demonstrate a decreasing effectiveness of fluoroquinolones in infections caused by resistant *Campylobacter* spp.,[2,17,24,29] and fluoroquinolone-resistant *Campylobacter* isolates are shed longer than susceptible isolates.[17] Fluoroquinolones reach high peak concentrations in feces: following standard oral doses, peak concentrations of norfloxacin range between 207 and 2,716 μg/g feces, exceeding largely those that are achieved in serum and the resistance breakpoints. This may explain clinical cure in cases of apparently resistant organisms.[38]

For the macrolides, there is growing evidence that infections caused by resistant *Campylobacter* isolates are associated with more serious and invasive infections compared to infections with susceptible isolates.[34]

In view of the potential treatment failure, fluoroquinolones should be replaced by macrolides when treatment for suspected *Campylobacter* enteritis is needed in a setting with high fluoroquinolone resistance. Likewise, the present data may add to the debate on the choice of antibiotic for travelers' diarrhea: the present information on regional fluoroquinolone resistance should be considered together with the risk of contracting *Campylobacter* enteritis and the indication for treatment.[39,40] For instance, the high prevalence of fluoroquinolone-resistant *Campylobacter* isolates in the Indian subcontinent and South-East Asia is of particular concern because these popular tourist regions also stand out for their risk for travelers to contract *Campylobacter* enteritis.[4,10,18]

In conclusion, the present study demonstrated high and rising norfloxacin resistance rates in *Campylobacter* isolates recovered from travelers on their return from Asia, Latin America, and Europe, and increasing resistance rates among isolates from travelers returning from Africa. Although limited, macrolide resistance showed an increase over time. The high resistance rates to fluoroquinolones warrant reconsideration of their use as drugs of choice in patients with severe gastroenteritis when *Campylobacter* is the presumed cause. Continued monitoring of the incidence and the spread of resistant *Campylobacter* isolates are warranted.

Declaration of Interests

The authors state that they have no conflicts of interest.

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