Antimicrobial Use: A Risk Factor or a Protective Factor for Acquiring Campylobacteriosis?

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Background. It is well acknowledged that the use of antimicrobial drugs in food animals leads to antimicrobial drug resistance in foodborne bacteria such as Campylobacter; however, the role of human antimicrobial usage is much less investigated. The aim of this study was to quantify the odds of campylobacteriosis conferred by human consumption of fluoroquinolones and macrolides.

Methods. We conducted a registry-based retrospective case-control study on 31,669 laboratory-confirmed cases of campylobacteriosis between 1999 and 2005 in Denmark. Data were obtained from several Danish databases: the National Registry of Enteric Pathogens, the Danish Civil Registration System, the Danish National Prescription Database, and the Integrated Database on Labor Market Research. Odds ratios (OR) for campylobacteriosis were calculated by conditional logistic regression.

Results. The risk of campylobacteriosis was reduced 1 month after exposure to macrolides (OR, 0.72; 95% confidence interval [CI], 0.56–0.92). Macrolide exposure 1 month to 2 years before infection was associated with an increased risk of a Campylobacter diagnosis (OR, 1.5; 95% CI, 1.4–1.6). A history of fluoroquinolone use was also associated with increased risk (OR, 2.5; 95% CI, 1.8–3.5). This risk was higher for resistant isolates than for susceptible ones.

Conclusions. Treatment with macrolides may protect against Campylobacter infection for a limited period of time, possibly due to the antibacterial effects of the drug or its metabolites. Fluoroquinolone treatment confers increased risk, probably due to a combination of competitive and selective effects, similar to what has been observed for nontyphoid Salmonella infection.

Campylobacter jejuni is recognized worldwide as the leading cause of bacterial gastroenteritis [1]. In 2008, a total of 190,566 campylobacteriosis cases were reported (overall incidence of 40.7 per 100,000) by 25 EU Member States [2]. The level of antimicrobial resistance of this bacterium has been rising for many years. Resistance against fluoroquinolones and macrolides is of particular concern for public health. A major source of human campylobacteriosis is poultry and products thereof, and several studies indicate that use of antimicrobials such as fluoroquinolones and macrolides in poultry production selects for drug-resistant Campylobacter [3–5]. Drug-resistant Campylobacter transferred to humans in the food chain may cause more severe illness than sensitive strains [6]. Less well understood and described is the role of human consumption of antimicrobial drugs. Only a few studies highlight the role of this consumption on the development of antimicrobial drug resistance in Campylobacter [7–9]. The vast majority of publications focus instead on the role of other risk factors, like travel association, consumption of chicken and other food products, contact with animals, and other factors [10–12].

In the present registry-based study, we evaluated the association between fluoroquinolones and macrolides prescribed in general practice on the occurrence of subsequent infection. We also estimated the odds of diagnosis with a resistant strain after exposure to a course of antimicrobials; we accomplished this by...
fitting an interaction term into the model between the odds of being diagnosed with campylobacteriosis and the odds of being diagnosed with a resistant strain.

**METHODS**

**Registers**

All culture-confirmed cases of *Campylobacter* are reported to the Statens Serum Institut (SSI) and entered into the National Registry for Enteric Pathogens [13]. This register only includes each patient’s first isolate within a time frame of 6 months; if the patient has another positive sample within this period, it is considered to be a recurrent or persistent infection and is discarded in the database. During the study period (1999–2005) 32.4% of 31 669 isolates reported to SSI were susceptibility tested against fluoroquinolones and macrolides. For these strains, we calculated excess odds of campylobacteriosis after drug exposure, as well as a multiplicative interaction term (the odds that the infective strain was resistant to the antimicrobial previously taken). For a more comprehensive testing of resistance, a total of 459 strains were tested for a broader panel of antimicrobial drugs (Table 1) as a part of the Danish Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP) surveillance scheme [16]. However, due to the low number of strains examined, we did not have statistical power to calculate the interaction term for these antimicrobials. The data were linked using the unique, personal identification number used in the Civil Registry System (CRS) [17]. Information on county of residence can directly be deduced from this database.

To obtain data on exposure to antimicrobial drugs prior to the *Campylobacter* infection, we used the National Prescription Database. This database contains information on all prescriptions provided by general practitioners, which were filled at pharmacies in Denmark. Data were once again linked using the Civil Registry System number and included the generic name of the drug, the ATC-code, dosage, price, and date of issue. To control for the confounding effect of education and socioeconomic status, we obtained data on schooling and income from the Integrated Database on Labor Market Research [18].

**Study Participation**

We included all laboratory-confirmed patients with campylobacteriosis between 1 January 1999 and 31 December 2005. For each case, we selected 10 controls from the Civil Registry System who were alive on the date the positive sample was received at the SSI and matched them to the case on sex, age, and county of residence. Data from the prescription database were available from 1 January 1995 until 31 December 2005.

We compared the history of antimicrobial use in *Campylobacter* patients to the history of use of their matched controls in a period up to 2 years prior to diagnosis.

**Susceptibility Testing**

The antimicrobial drugs of interest for this study were fluoroquinolones and macrolides. To simplify the analysis, strains that were resistant against nalidixic acid and/or ciprofloxacin were considered resistant against fluoroquinolones; strains that were resistant against erythromycin were considered resistant against macrolides. All strains that were typed “intermediate” resistant were considered to be susceptible. All antimicrobial susceptibility testing was performed with a commercially available MIC technique (Sensititre, Trek Diagnostic Systems Ltd). The cells were inoculated and incubated according to the CLSI guidelines. The breakpoints for this testing have changed over the years and can be found in the annual DANMAP reports (www.danmap.dk) [19].

**Data Analyses**

We conducted a registry-based, matched, retrospective case-control study. For this purpose, we defined an index date as the date 21 days before the date when the sample was entered

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**Table 1. Definition of the Groups of Antimicrobials Used in This Study**

<table>
<thead>
<tr>
<th>Antimicrobials for which the excess risk of campylobacteriosis and the interaction term was calculated</th>
<th>ATC code</th>
<th>Antimicrobials susceptibility tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones</td>
<td>J01M</td>
<td>Ciprofloxacin, nalidixic acid</td>
</tr>
<tr>
<td>Macrolides</td>
<td>J01F</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>J01GB</td>
<td>Streptomycin, gentamicin, apramycin, kanamycin, spectinomycin</td>
</tr>
<tr>
<td>Amphenicols</td>
<td>J01B</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Other antibacterials</td>
<td>J01X</td>
<td>Nitrofurantoin, polymyxin</td>
</tr>
<tr>
<td>Sulfonamids and Trimethoprim</td>
<td>J01E</td>
<td>Sulfamethoxazole, trimethoprim</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>J01A</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>Third generation cephalosporins</td>
<td>J01DD</td>
<td>Ceftriaxion</td>
</tr>
</tbody>
</table>

Breakpoints used in this study for susceptibility testing are different per year: see DANMAP1997 [14] and —DANMAP2005 [15].
in the National Registry for Enteric Pathogens. These 21 days are composed of 2 time-intervals: first, a 7-day average between the visit to the general practitioner’s office or admission to hospital, and the date the sample was entered in the database; and second, the 14 days we consider the “acute phase” of infection. Antimicrobial drugs prescribed in this acute phase are likely to be prescribed for early empirical treatment of the Campylobacter infection, and therefore causes protopathic bias [20]. Drugs taken in this time frame were excluded from the main analysis but were included in an additional sub-analysis described later.

In the main part of the analysis, we examined the odds of exposure to a course of antimicrobials before being diagnosed with Campylobacter, from the index date to 1 year before onset of disease. We also calculated the odds of a strain being resistant against the antimicrobial taken. Odds ratios (ORs) for exposure to antimicrobial drugs before infection were calculated using a conditional logistic regression model; Table 1 outlines the categorization of antimicrobial drugs.

In the second part of the study, we calculated a time-dependent OR for exposure to antimicrobials in 6 different time intervals before infection. The OR was estimated as a function of time before onset of infection. In addition, we applied cubic splines [21] to obtain a smooth curve (Figure 1). The coefficients for the cubic spline function were estimated in a conditional logistic regression model. In the cubic spline model 3 knot points were used; these were chosen to be at 60 d, a half year, and 1 year before onset of infection. A knot point is a point where the coefficients for the third-degree polynomial were allowed to change, although only under the restriction that the curve has to be continuous and smooth in the knot points.

The time frames were the “acute phase,” 0–2 weeks, 2–4 weeks, 1–6 months, 6–12 months, and 1–2 years before index date. All of the estimated ORs were adjusted for rural/urban differences by population density (separated in 5 categories: >2000, 1001–2000, 351–1000, 26–350, 1–25 persons per square kilometer), schooling (primary school or more than primary school), and income (income per household/number of adults in the household matched within 100 000 dkk (~19 000 USD intervals) [13].

All analyses were performed using conditional logistic regression with the PROC PHREG- procedure in SAS 9.1 for Windows (SAS Institute).

**RESULTS**

In the study period, a total of 31 669 Campylobacter cases were reported, of which 10 275 were susceptibility tested for both fluoroquinolones and macrolides. These 10,275 patients were matched (1:10) to 97 523 controls. Overall, 21.7% was resistant against fluoroquinolones and 2.3% against macrolides (Table 2). The prevalence of fluoroquinolone resistance was highest in adults 50–59 years of age and lowest in children. A smaller sample was additionally tested for susceptibility to aminoglycosides, amphenicols, other antibacterials (ATC-code J01X), sulfonamids and trimethoprim, tetracyclines, and third-generation cephalosporins.

Being diagnosed with campylobacteriosis was associated with an increased odds of exposure to a course of fluoroquinolones, macrolides, sulfonamids and trimethoprim, tetracyclines, and broad spectrum penicillins up to 1 year before onset of disease (Table 3). This risk was highest for taking fluoroquinolones (OR, 2.4; 95% CI, 1.97–2.97). For fluoroquinolones, we found an effect modification, that is, resistant strains conferred a higher risk of diagnosis than susceptible strains. The odds of being exposed to a course of fluoroquinolones was 2.4 times higher for cases diagnosed with a fluoroquinolone-sensitive Campylobacter than for controls, whereas the odds of being exposed to fluoroquinolones was 3.8 (2.4 × 1.6) times higher for cases with a fluoroquinolone-resistant Campylobacter than for controls. The logistic regression model is multiplicative, and the product in the brackets is the main effect (OR 2.4 for susceptible strains) multiplied by the interaction term (OR 1.6 for the tested strain being resistant to the antimicrobial taken). There was no interaction between macrolide exposure and macrolide resistance.

In the second analysis of this study, we calculated the risk (OR) of previous exposure to antimicrobials in different time intervals for people who had been diagnosed with Campylobacter. The results of this analysis are given in Figure 1. This graph shows the OR, plotted against the time since last antimicrobial exposure before infection with Campylobacter, in cubic splines. The results for fluoroquinolones and macrolides were different. Diagnosis with Campylobacter was associated with a decreased odds of macrolide consumption in the period close to diagnosis, while it was associated with an increased fluoroquinolone consumption in the same period (Table 4). We examined the effect of macrolides more thoroughly to determine the duration of this protective effect and performed the analyses for 4 different macrolides separately; erythromycin, roxithromycin, clarithromycin, and azithromycin. There was an excess odds of consumption of each of these drugs up to 1 year before infection (Table 4). However, if the time between last exposure and Campylobacter infection is reduced to only the acute phase of infection (the estimated time before onset of disease and appearance in our database), exposure to macrolides became a protective factor (OR .72, up to 1 month before infection; Table 4).

**DISCUSSION**

We have recently shown that a history of use of several different classes of drugs is associated with an excess risk of being diagnosed with nontyphoid Salmonella [22]. Furthermore, this
Figure 1. Cubic spline plots of the odds ratio (OR) of being exposed to macrolides and fluoroquinolones 0–2 years before infection with *Campylobacter*, 1997–2005 Denmark. The ORs are adjusted for sex, age, county of residence, population density, income, and schooling.

Table 2. Age Distribution and Prevalence of Resistance in 10475 *Campylobacter* Strains Examined for Susceptibility for Fluoroquinolones and Macrolides, Denmark, 1999–2005

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Total no. of patients N (%)</th>
<th>No. and % susceptibility testeda N (%)</th>
<th>Fluoroquinolone resistanceb N (%)</th>
<th>Macrolide resistancec N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–9 years</td>
<td>4076 (14.9)</td>
<td>1556 (38.2)</td>
<td>224 (14.4)</td>
<td>25 (1.6)</td>
</tr>
<tr>
<td>10–19 years</td>
<td>3039 (11.1)</td>
<td>1150 (37.8)</td>
<td>231 (20.1)</td>
<td>21 (1.8)</td>
</tr>
<tr>
<td>20–29 years</td>
<td>6841 (25.1)</td>
<td>2750 (40.2)</td>
<td>613 (22.3)</td>
<td>57 (2.1)</td>
</tr>
<tr>
<td>30–39 years</td>
<td>4971 (18.2)</td>
<td>1958 (39.4)</td>
<td>428 (21.9)</td>
<td>40 (2.0)</td>
</tr>
<tr>
<td>40–49 years</td>
<td>3117 (11.4)</td>
<td>1098 (35.2)</td>
<td>281 (25.6)</td>
<td>32 (2.9)</td>
</tr>
<tr>
<td>50–59 years</td>
<td>2505 (9.2)</td>
<td>992 (39.6)</td>
<td>256 (25.8)</td>
<td>32 (3.2)</td>
</tr>
<tr>
<td>60–69 years</td>
<td>1436 (5.2)</td>
<td>542 (37.7)</td>
<td>137 (25.3)</td>
<td>21 (3.9)</td>
</tr>
<tr>
<td>70–79 years</td>
<td>835 (3.1)</td>
<td>293 (35.1)</td>
<td>72 (24.6)</td>
<td>8 (2.7)</td>
</tr>
<tr>
<td>80 and older</td>
<td>456 (1.7)</td>
<td>136 (29.8)</td>
<td>26 (19.1)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Total</td>
<td>27,276 (100)</td>
<td>10,475 (38.4)</td>
<td>2268 (21.7)</td>
<td>238 (2.3)</td>
</tr>
</tbody>
</table>

*a* Overall $\chi^2$: 45.0, degrees of freedom: 8, $P$ value: <.001.

*b* Overall $\chi^2$: 69.8, degrees of freedom: 8, $P$ value: <.001.

*c* Overall $\chi^2$: 14.8, degrees of freedom: 8, $P$ value: .06.
effect was substantially modified by the resistance pattern of the infecting strain [22]. This finding strongly supports the idea of competitive and selective effects of antimicrobial drug use [23, 24]. The results of the present study are in line with the fluoroquinolone findings in our Salmonella study, as well as our observation that a history of human antimicrobial-drug exposure may constitute a long-term risk for being diagnosed with Campylobacter. Surprisingly, in the current study, diagnosis with Campylobacter was associated with a reduced odds of recent history of macrolides compared with controls. This raises the hypothesis that macrolide use may protect against Campylobacter infection for a limited period of time, perhaps as long as 4–8 weeks (Table 4).

To assess this hypothesis, different effects of antimicrobial drugs should be considered, including their spectrum, the antibacterial effect of their metabolites, and their pharmacokinetics. The pharmacokinetics of macrolides are well described in the literature; the half-life of macrolides is different for each of the drugs included in this study; erythromycin has a short half-life (<4 hours), roxithromycin and clarithromycin an intermediate half life (4–24 hours) and azithromycin has a long half-life (>72 hours) [25]. However, the protective effect of the drugs last at least 4 weeks (Figure 1). The effect of macrolides, as a group, in the acute phase and 0–2 weeks before the index date (OR, .72; 95% CI, .56, .92) is strong. The acute phase exposure may constitute a long-term risk for being diagnosed with Campylobacter.

It is interesting that a protective effect is seen in all the macrolides (Table 4), even though the kinetics of each of the macrolides is quite different. One explanation for this phenomenon is that macrolides, especially azithromycin, become trapped in the intracellular lysosomes of phagocytic cells. This intracellular uptake is easily reversible for erythromycin and clarithromycin but is extremely slow and probably not completely reversible for azithromycin [26, 27]. It is even possible

### Table 3. Risk of Campylobacter Diagnosis by Exposure to a Course of Antimicrobial Drugs 0–12 Months Before Infection, Denmark, 1999–2005

<table>
<thead>
<tr>
<th>Exposed to (up to 1 year before infection):</th>
<th>No. (%) exposed cases/controls</th>
<th>Risk for campylobacteriosis after exposure (main effect) OR (95% CI)</th>
<th>OR for resistant strain a,b (interaction term) OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases (10275)</strong></td>
<td><strong>Controls (97591)</strong></td>
<td><strong>P</strong></td>
<td><strong>P</strong></td>
</tr>
<tr>
<td>Broad-spectrum penicillins</td>
<td>1191 (11.6)</td>
<td>8756 (9.0)</td>
<td>1.35 (1.25, 1.45)</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>183 (1.8)</td>
<td>658 (0.7)</td>
<td>2.42 (1.96, 2.98)</td>
</tr>
<tr>
<td>Sulfanomids and Trimethoprim</td>
<td>530 (5.1)</td>
<td>3535 (3.6)</td>
<td>1.48 (1.34, 1.64)</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>202 (2.0)</td>
<td>1437 (1.5)</td>
<td>1.36 (1.16, 1.59)</td>
</tr>
<tr>
<td>Macrolides</td>
<td>1158 (11.3)</td>
<td>7642 (7.8)</td>
<td>1.48 (1.38, 1.59)</td>
</tr>
</tbody>
</table>

The odds ratios (ORs) were adjusted for sex, age, county of residence, level of schooling, income, and population density.

a Cases that were exposed to antimicrobials 1 year before infection (and were infected with a strain that was resistant to the drug previously taken).

b Statistically, this was fitted as an interaction term, the total relative risk for infection with a drug-resistant Campylobacter that is resistant to the drug previously taken can be estimated as the product of the 2 ORs.

### Table 4. Risk of Campylobacter Diagnosis by Timing of Exposure to a Course of Antimicrobials 0–12 Months Before Infection, Denmark, 1999–2005

<table>
<thead>
<tr>
<th>Exposed to:</th>
<th>Upto 1 year before infection a</th>
<th>Upto 3 months before infection b</th>
<th>Upto 2 months before infection c</th>
<th>Upto 1 month before infection c</th>
<th>Only the acute phase: OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin</td>
<td>1.40 (1.25–1.57)</td>
<td><em>P</em> = .001</td>
<td>Not enough power for the separated analyses</td>
<td>0.06 (0.01–0.43)</td>
<td><em>P</em> = .005</td>
</tr>
<tr>
<td>Roxithromycin</td>
<td>1.63 (1.37–1.93)</td>
<td><em>P</em> = .001</td>
<td>0.39 (0.09–1.63)</td>
<td><em>P</em> = .20</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>1.62 (1.29–2.02)</td>
<td><em>P</em> = .001</td>
<td>0.83 (0.25–2.71)</td>
<td><em>P</em> = .75</td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>1.44 (1.30–1.60)</td>
<td><em>P</em> = .001</td>
<td>0.29 (0.11–0.79)</td>
<td><em>P</em> = .02</td>
<td></td>
</tr>
<tr>
<td>Macrolides grouped</td>
<td>1.48 (1.38–1.59)</td>
<td><em>P</em> = .001</td>
<td>1.16 (1.02–1.31)</td>
<td><em>P</em> = .02</td>
<td>0.98 (0.83–1.16)</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>2.42 (1.96–2.98)</td>
<td><em>P</em> = .001</td>
<td>2.54 (1.83–3.54)</td>
<td><em>P</em> = .001</td>
<td>2.65 (1.78–3.93)</td>
</tr>
</tbody>
</table>

The odds ratios (ORs) were adjusted for sex, age county of residence, level of schooling, income, and population density.

a This period does not include the “acute phase” of infection.

b These periods do include the “acute phase” of infection.
that part of the azithromycin metabolites remain trapped in the lysosome until the cell dies, and the drug is finally released (N. Frimodt-Møller, personal communication, 2009).

Antimicrobial drug promoters, given to food animals in subinhibitory concentrations, may have profound effects on the intestinal flora and risk of infection with gastrointestinal infections. It cannot be ruled out that macrolides or their metabolites are present in intestines of humans for several weeks in sufficiently high concentrations to produce a similar effect. This may be the case for azithromycin, as well as other drugs. Clearly, additional studies are needed to examine this possibility. Other explanations for our observation should be considered. Although macrolides are mostly prescribed in the winter season for respiratory infections, and Campylobacter infections are most common in the late summer [28, 29], confounding effects by season are not a likely explanation for the association because we adjusted for season by matching on the index date of the case. Furthermore, several other classes of antimicrobial drugs are prescribed more commonly in the winter season as well, without causing a similar pattern [22].

For fluoroquinolones, we found a risk pattern similar to the risk pattern found when examining their effects with nontyphoid Salmonella infection [22]. The observation, as shown in Figure 1, can be ascribed to a combination of 3 effects: the “competitive effect,” the “selective effect,” and for fluoroquinolones, also the effect of treatment (protopathic bias). The effect of treatment can be seen in the ‘acute phase’ of the infection where the patient might have received a course of fluoroquinolones as early empirical treatment, before the stool-sample was taken. The competitive effect is independent of the susceptibility pattern and can be explained by depletion of the normal gut-flora, thereby leaving the person susceptible to a smaller dose of an infective agent, in this case Campylobacter. Finally, the selective effect is the advantage to resistant Campylobacter strains already colonizing the gut when the antimicrobial was taken [23, 24].

We assume that the observed effect in Figure 1, from a point where the line stabilizes (at ~3 months before infection for macrolides and a year for the fluoroquinolones) can be considered as a base-line for “selection bias” (the effect that some people are more likely to be tested than other people). A history of drug use may also be an indicator of increased use of health care (and thus a marker of frailty) and therefore might contribute to this effect [30]. Furthermore, an asymptomatic Campylobacter carrier may develop diarrhea due to the non-specific effect of the antibiotic and may be sampled based on this. However, it cannot be completely ruled out that some antimicrobial drugs may have a long-term effect on the gut flora and thus render patients more susceptible to campylobacteriosis.

We found some differences in the number of samples susceptibility-tested in each age-group (Table 2). Even though the differences are significant, we assume that this is due to random error. We also found a significant difference in the number and percentages of fluoroquinolone-resistant individuals for different age groups. This effect is likely to be explained by 2 factors: (1) the fact that it is not common to prescribe fluoroquinolones to children and (2) the differences in travel behavior between the age groups. In 2008, 27.4% of Campylobacter cases were travel related [31] and were associated with a higher percentage of resistance [16]. However, matching for age should have eliminated any related bias.

The study is subject to some limitations. First, some antimicrobial drugs are mainly used in hospital settings, and these data are not included in the Danish prescription database. However, in Denmark, 90% of the prescribed antimicrobials are prescribed in the primary health sector [16]. We can only speculate that the impact of these antimicrobials would have been larger if they were included in the study.

Second, it is well known that Campylobacter shows immense antigenic diversity, and immune-evasion strategies can differ greatly between different strains of Campylobacter [32]. Unfortunately, species identification and subtyping of Campylobacter is not carried out as a routine activity in Denmark; therefore, these data were not available for use.

To conclude, human use of broad-spectrum penicillins, sulfonamids, trimethoprim, tetracyclines, macrolides, and in particular fluoroquinolones may form a risk factor for acquiring campylobacteriosis. Furthermore, fluoroquinolone consumption selects for infection with resistant Campylobacter. To our surprise, Campylobacter diagnosis was associated with a reduced odds of recent macrolide use.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References