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# Regional and seasonal differences in incidence and antibiotic resistance of *Campylobacter* from a nationwide surveillance study in The Netherlands: an overview of 2000–2004

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## ABSTRACT

*Campylobacter* is the most common cause of bacterial gastroenteritis worldwide. This study describes regional and seasonal differences among culture-proven *Campylobacter* infections in The Netherlands in 2000–2004. Data were used from two ongoing projects in The Netherlands, covering 3 million and 8 million inhabitants, respectively, for surveillance of infectious diseases. The incidence of *Campylobacter* infection was highest in the south of The Netherlands (55.7/100 000 vs. an average of 39.1/100 000 in other regions). The incidence in urbanised areas was 41.9/100 000 vs. 32.4/100 000 in rural areas. High stable rates of resistance to fluoroquinolones (35%) were observed. Resistance to erythromycin increased from 1.9% (in 2001) to 2.7% (in 2004). The highest rates of resistance to erythromycin were found in the south. Resistance rates increased with increasing urbanisation, most obviously for fluoroquinolones (35.9% urban vs. 27.10% rural). An inverse relationship was observed between the incidence of infection (high in summer, low in winter) and resistance to both fluoroquinolones and macrolides. Resistance to fluoroquinolones was higher in travel-related infections (54%) than in endemic infections (33%). Differences in regional incidence and resistance rates of *Campylobacter* infections were found. Foreign travel appeared to be associated with higher resistance rates. Given the high fluoroquinolone resistance rate, empirical treatment of severe, microbiologically confirmed, *Campylobacter* infection with a fluoroquinolone should be discouraged, pending susceptibility testing.

**Keywords** *Campylobacter*, fluoroquinolone resistance, macrolide resistance, seasonal variation, urbanisation

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## INTRODUCTION

Infections with *Campylobacter* spp. are the most frequent cause of bacterial gastroenteritis in industrialised and developing countries worldwide [1–5]. The number of infections has risen several-fold during the past two decades. A consensus seems to have emerged that this rise is caused largely by increased consumption of poultry meat [6,7]. Most often, infections with *Campylobacter* spp. cause a self-limiting diarrhoeal illness and need not be treated with antimicrobial agents, although *Campylobacter* infections may be followed by severe complications [8]. Antimicrobial therapy is necessary for patients with severe and prolonged enteritis (particularly neonates and elderly individuals), suspected septicaemia, other invasive extra-intestinal manifestations, and patients with a severe underlying illness (e.g., hypo- or agammaglobulinaemia or human immunodeficiency virus infection). Drugs of choice include ciprofloxacin [9] for early empirical treatment of adults, especially for travel-related disease, and erythromycin for treatment following microbiological confirmation [1,10].

During the 1990s, resistance to fluoroquinolones among *Campylobacter* spp. increased significantly in The Netherlands and other European countries [11,12]. The increase in quinolone

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resistance has been associated with the introduction of fluoroquinolones into veterinary medicine during the late 1980s and early 1990s [11–13], especially for poultry. A previous regional surveillance study in The Netherlands demonstrated an increase in fluoroquinolone-resistant campylobacters, from 15% in 1992 to >30% in 2003 [14]. This was an alarming increase, since, among other reasons, patients infected with ciprofloxacin-resistant *Campylobacter* strains may have a six-fold increased risk of invasive illness or death compared with patients infected with ciprofloxacin-susceptible *Campylobacter* strains [4]. The present study describes a nationwide epidemiological analysis of culture-proven *Campylobacter* infections in The Netherlands during 2000–2004.

## PATIENTS AND METHODS

Data from two ongoing projects for surveillance of infectious diseases in The Netherlands were used.

### Laboratory surveillance system (LSI)

Since 1995, 15 regional public health laboratories have reported weekly to the National Institute for Public Health and the Environment (Bilthoven, The Netherlands) concerning the total number of first isolates of *Campylobacter* spp., as well as other bacterial pathogens, and the total number of faecal samples under investigation. These 15 laboratories are situated in all regions of The Netherlands and cover *c.* 50% of the 16 million inhabitants. Since 2002, information concerning the species and antibiotic resistance against fluoroquinolones, tetracyclines and erythromycin, and data concerning patient age, gender, place of residence and recent foreign travel, have been reported periodically for each first isolate.

### Infectious disease surveillance information system

In 1994, the National Institute for Public Health and the Environment developed a computer-based centralised data system called the 'infectious diseases surveillance information system' (ISIS). ISIS consists of a steadily expanding network of sentinel laboratories. Early in 2000, seven laboratories participated, covering 2.6 million inhabitants. During the year 2000, another three laboratories joined, and since 2001, ten more laboratories, situated in the middle and south of The Netherlands have participated, covering 3.3 million inhabitants. Participating laboratories transmit electronically all new results of microbiological investigations to ISIS on a daily basis. In contrast to most surveillance systems, both positive and negative laboratory results are recorded. All test results are anonymously and uniquely coded for each patient. Data accompanying the laboratory results include information from the laboratory request form, e.g., age, gender, place of residence, type of material sampled, type of investigation, test results, whether the request came from a general practitioner, specialist or outpatient clinic, and information concerning the strain and its antibiotic resistance. Information concerning foreign travel is not available from ISIS. For laboratory test results, a *Campylobacter* infection was recorded if a faecal culture was positive for *Campylobacter*. In order to include only one isolate per disease episode, only the first positive sample from each patient during a 6-month period was included in the analyses.

### Analyses

Results are presented for the period 2000–2004. Analysis was performed at the genus level only, but previous results indicate that 94% of isolates were *Campylobacter jejuni* [15–17].

Demographical information, e.g., age and gender, was obtained from ISIS for individuals with either positive or negative test results. Age groups were categorised, on the basis of definitions used previously [18], as 0–4, 5–14, 15–29, 30–44, 45–59 and ≥60 years. Positive and negative test results were analysed separately according to age and gender.

Geographical information was most complete for LSI surveillance, since the laboratories participating in LSI covered all geographical regions of The Netherlands. For each year, population size by municipality was obtained from Statistic Netherlands, and incidences were calculated, with the appropriate denominators adjusted for the degree of coverage. Incidence and resistance rates were analysed according to the level of urbanisation [14], defined on a scale from 1 (large cities, >2500 residences/km$^2$) to 5 (rural municipalities, <500 residences/km$^2$). Each urbanisation class represented *c.* 20% of the Dutch population.

In the ISIS database, seasonal variation in the incidence of *Campylobacter* infection was analysed for 2000–2004, and susceptibility to antibiotics was analysed for 2001–2004. Susceptibility data have been complete since 2001.

Recent foreign travel was reported only in the LSI project, and these data were used to study variation in antibiotic susceptibility among *Campylobacter* isolates from individuals with and without a history of recent foreign travel.

Susceptibilities of *Campylobacter* spp. were determined for fluoroquinolones (ciprofloxacin, ofloxacin and/or norfloxacin), macrolides (erythromycin or clarithromycin) and tetracyclines (tetracycline or doxycycline).

### Statistics

Differences among rates were judged by their relative risk (RR), using a 95% CI.

## RESULTS

### Demographics

During the LSI project in 2000–2004, 16 706 campylobacters were reported, whereas 4501 of the 73 325 samples tested in the ISIS project were positive for *Campylobacter*. During 2004, >13 000 faecal samples were tested for *Campylobacter* in the laboratories participating in ISIS, of which 885 (6.3%) were positive. Female patients were tested more frequently for *Campylobacter* than were males (1.2:1), but male patients tested for faecal