

# Local outbreak of quinolone-resistant but ceftriaxone-susceptible gonorrhoea in a region of Denmark

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## ABSTRACT

**INTRODUCTION:** During the past decade, gonorrhoea has been on the rise in several European countries; and along with a decreasing susceptibility to currently used antimicrobial agents, there are worldwide concerns about future case management. The objective of the present study was to describe the antibiotic resistance of gonococci and physicians' adherence to national Danish guidelines in the Region of Northern Jutland (RNJ) from 2000 to 2010.

**MATERIAL AND METHODS:** All incident episodes of microbiologically confirmed *Neisseria gonorrhoeae* infections from 2000 to 2010 were included. Data were retrieved from the Laboratory Information System at the Department of Clinical Microbiology, Aalborg University Hospital. Clinical data on hospital-treated patients were retrieved from medical records. General practitioners and patients were not contacted.

**RESULTS:** A total of 296 incident episodes in 285 patients were included. The majority of infections were observed in men (71%). The annual incidence increased five-fold during the study period and peaked in 2009. Most infections were acquired in Denmark. Thirteen per cent had swabs performed according to guidelines from the Danish National Board of Health. Quinolone-resistance fluctuated between 13% and 93%. The highest level was observed in 2009. No isolates were resistant to ceftriaxone and we observed no treatment failure.

**CONCLUSION:** We have described a local outbreak of quinolone-resistant but ceftriaxone-susceptible gonorrhoea in the RNJ. Our study highlights the importance of microbiological confirmation, treatment and follow-up of gonorrhoea in accordance with national guidelines.

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Gonorrhoea continues to present a public health problem worldwide with an estimated 106 million persons infected annually [1]. In men, infection of the urethra is often symptomatic. In women, infection of the endocervix is often asymptomatic, as are rectal and pharyngeal infections in both men and women [2]. Untreated infections may cause severe morbidity and may contribute to HIV transmission.

Following the AIDS epidemic in the 1980s, a marked reduction in the incidence of gonorrhoea was noted in Denmark and many other countries [3]. Several European countries, including Denmark, have reported a rising incidence of the infection over the past decade, particularly among men who have sex with men (MSM) [4, 5] and heterosexuals aged 15-25 [6, 7]. *Neisseria gonorrhoeae* has developed resistance to a broad spectrum of antimicrobial agents used for treatment, including penicillin, azithromycin, tetracycline and quinolones. At present, a third generation cephalosporin is first-choice empirical treatment for gonorrhoea in many countries, including Denmark [6, 8, 9]. However, antimicrobial resistance to third generation cephalosporins has been reported [10]. In the USA, Centers for Disease Control and Prevention now recommend dual therapy for treatment of uncomplicated gonorrhoea. Developing antibiotic resistance poses an ongoing challenge for successful case management [11].

In recent years, the Danish Region of Northern Jutland (RNJ) has experienced an outbreak of quinolone-resistant gonorrhoea. The aim of the present study was to describe the epidemiology and antibiotic resistance of *N. gonorrhoeae* in the RNJ from 2000 to 2010, and to evaluate adherence to national case management guidelines.

## MATERIAL AND METHODS

A population-based observational study was performed in the RNJ covering the 2000 to 2010 period. On 1 January 2007, the 13 Danish counties were replaced by five larger regions. The borders of the former North Jutland County falls within the present RNJ. Therefore, the mixed urban/rural study area comprised ~ 495,000 inhabitants from 2000-2006 and ~ 580,000 inhabitants from 2007-2010. It further comprised 355-380 general practitioners (GPs) and six hospitals that provided tax-paid health service to all residents. The Department of Clinical Microbiology (DCM) at Aalborg University Hospital performed all microbiological tests in the region.

## Patients and sample collection

All incident episodes of microbiologically confirmed *N. gonorrhoeae* infections were identified and retrieved

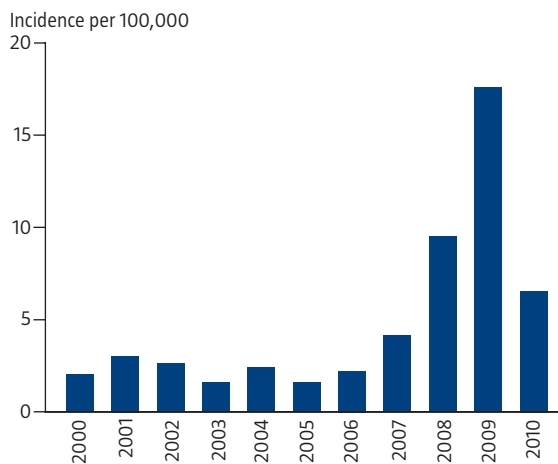
## ORIGINAL ARTICLE

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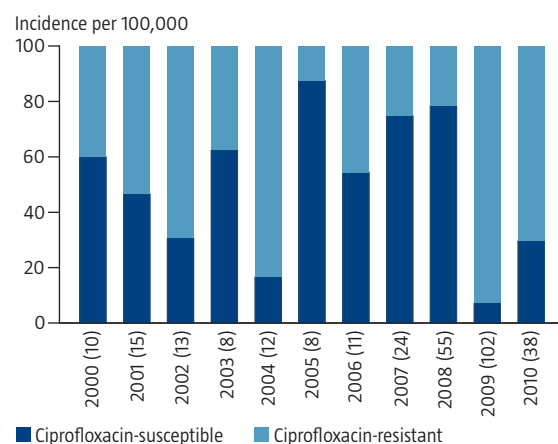
**FIGURE 1**

Annual incidence of gonorrhoea in Northern Jutland, 2000-2010.



**FIGURE 2**

Antimicrobial susceptibility to ciprofloxacin in *Neisseria gonorrhoeae* and number of isolates (n) in the Region of Northern Jutland, 2000-2010.



from the Laboratory Information System (ADBact; Autonik, Sködinge, Sweden) in the DCM. *N. gonorrhoeae* was detected in patient samples by culture. Antigen testing, nucleic acid amplification technique or direct microscopy of Gram-stained smear was not performed in the study period. Data on anatomical sampling site(s), antimicrobial susceptibility, follow-up cultures and *Chlamydia trachomatis* co-infection were retrieved from the same source. Information on age, gender, sexual orientation and travel history was obtained from medical records related to the ceftriaxone treatment at the Department of Infectious Diseases (DID) Aalborg University Hospital, or medical treatment at other departments for complaints related to gonorrhoea. Patients treated in

the DID were informed about the importance of test of cure (TOC). Likewise, GPs were informed about TOC when contacted by the DCM concerning a positive *N. gonorrhoeae* culture.

GPs and patients were not contacted for further information. Travel history was not a routine question, but had been registered when reported by the patients. HIV testing was not routinely performed.

Only incident episodes were included. An incident episode was defined as an episode with either  $\geq 4$  weeks since the last episode, or  $< 4$  weeks and a negative test since the last episode. Three patients had two culture-positive episodes within one month and no test of cure in-between. For each of these patients, we decided to register one incident episode.

### Susceptibility testing

Susceptibility to antibiotics was routinely determined for penicillin, ciprofloxacin and ceftriaxone by the Epsilon-ometer test (E-test) method (AB Biodisk, Solna, Sweden). All isolates, except ten, were sent to the Neisseria and Streptococcus Reference Laboratory (Statens Serum Institut, Copenhagen) to confirm susceptibility. An isolate was reported susceptible or resistant according to the present European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints, except for penicillin that until December 2006 was reported susceptible at a minimum inhibitory concentration  $\leq 0.125$   $\mu\text{g}/\text{ml}$ . In case of beta-lactam allergy, susceptibility testing was made for chloramphenicol, gentamicin, co-trimoxazole, clarithromycin, tetracycline and carbapenems.

Patients infected with isolates sensitive to both penicillin and ciprofloxacin were treated in general practice, while most patients infected with resistant strains were referred to the DID, for ceftriaxone treatment.

### Statistical analysis

Study data were entered into EpiData (EpiData Association, Odense, Denmark), and Stata 11.2 for Windows (StataCorp, College Station, TX, USA) was used for all analyses. Fisher's exact test was used for categorical data and the Mann-Whitney U test for continuous data. A p-value  $< 0.05$  was considered statistically significant. Annual incidence rates were calculated with population data from Statistics Denmark in the denominator.

The study was conducted according to the guidelines of the regional scientific ethics committee for use of clinical and laboratory data and registered by the RNJ.

*Trial registration:* not relevant.

### RESULTS

A total of 296 incident episodes from 285 patients (201



TABLE 1

Proportion of episodes with swabs performed according to guidelines from the Danish National Board of Health (three swabs for men and four for women). The values are n/N (%).

	Men	Women	p-value <sup>a</sup>
Primary visit	19/209 (9)	20/87 (23)	0.004
2000-2007	4/77 (6)	3/24 (13)	0.02
2008-2010	15/132 (11)	17/63 (27)	
Follow-up visit	64/126 (51)	31/68 (46)	0.41

a) Statistical test for men versus women or 2000-2007 versus 2008-2010.

males and 84 females) were included. The majority of infections were observed in men (71%). The male/female ratio was 2.4. The majority of patients (275/285 = 96%) had one diagnosed episode of gonorrhoea during the study period, whereas nine patients had two episodes and one patient had three episodes. None of these episodes were considered treatment failure.

The annual incidence of gonorrhoea increased five-fold during the study period from 2-4 per 100,000 inhabitants in 2000-2007 to 17 per 100,000 inhabitants in 2009 (Figure 1).

Initial swabs were performed in accordance with the Danish National Board of Health (DNBH) guidelines in nine per cent of male episodes and 23% of female episodes ( $p = 0.004$ ). The highest accordance to guidelines was seen in the latter part of the period ( $p = 0.02$ ) (Table 1). Six per cent (men and women) had positive initial swabs from non-genital sites (pharynx and/or anus). On average, the GPs performed 1.5 samples per patient.

Follow-up swabs were performed more frequently in female patients ( $p = 0.003$ ) (Table 2) than in male patients. Swabs according to the DNBH guidelines were performed in 49% of cases with no gender difference (Table 1). An additional chlamydial swab was performed in 79% of cases, and 18% of these were positive with no gender difference.

Optional information on why a GP chose to perform a test for gonorrhoea was given in 56% of episodes. Among men, a local symptom (urethral discharge and/or dysuria) was the most common reason for a gonorrhoea test (55% of male patients). In female patients, local symptoms (vaginal discharge, pelvic pain and/or urethral discharge) were the reason for 30% of gonorrhoea tests. 30% of female patients were asymptomatic, but were tested for gonorrhoea because of contact to a gonorrhoea-positive person. This was indicated as the situation in one male episode.

Fluoroquinolone-resistance fluctuated between 13% and 93%, with the highest level being observed in 2009 (Figure 2). On average, 90% of the isolates were resistant to penicillin. No isolates were resistant to cef-



TABLE 2

Characteristics of incident episodes of gonorrhoea, Northern Jutland, 2000-2010.

	Men (n = 209)	Women (n = 87)	p-value
Age, yrs, median (IQR)	26 (14)	22 (8)	< 0.0001
Country of acquisition, n (%)			
Denmark, Greenland or unknown	181 (87)	85 (98)	0.003
Foreign	28 (13)	2 (2)	–
Swabs according to anatomical site, n (%)			
Anus	23 (11)	28 (32)	< 0.0001
Cervix	–	82 (94)	–
Pharynx	30 (14)	27 (31)	0.002
Urethra	208 (> 99)	42 (48)	< 0.0001
Any non-genital	33 (16)	30 (34)	0.006
Swab for <i>C. trachomatis</i> , n (%)	165 (79)	70 (80)	0.88
Concurrent chlamydia infection, n (%)	27 (16)	15 (21)	0.36
Follow-up swab for <i>N. gonorrhoea</i> , n (%)	126 (60)	68 (78)	0.003

IQR = interquartile range.

a) Percentage and significance test according to number of episodes with chlamydia swabs performed.

triaxone. All episodes of fluoroquinolone-resistance were treated with single-dose intramuscular ceftriaxone or (in two cases of allergy) with 7 mg/kg intravenous gentamicine. We observed no cases of treatment failure, although not all patients returned for follow-up examination.

## DISCUSSION

The epidemiology of gonorrhoea can change rapidly within a population. To counter the need for alterations in treatment recommendations continuous surveillance is necessary. In the first part of our study-period, the RNJ had a low incidence of gonorrhoea (2-4/100,000), which increased (to 17/100,000) due to a local outbreak in 2008-2009. We found 296 cases of culture-positive *N. gonorrhoeae* in the RNJ in the period. The male/female ratio was 2.4, which correlates with former evaluations [4]. The age distribution of cases was in accordance with national data [5]. In contrast to major cities worldwide, where MSM and HIV association may be driving a large part of gonorrhoeal transmission [12-14], this was not the case in our population. We had no routine information on HIV testing in our cohort, but the RNJ is a low-prevalence area for HIV infection (30/100,000 residents).

The proportion of patients with extra-genital gonorrhoea may vary with the patient population and with the setting, e.g. higher proportions are reported from dedicated clinics for genitourinary infections [8] than from GPs [15]. In a previous publication from Copenhagen, 6% of patients managed in general practice had optimal sampling [15], whereas our results showed that 9% of men and 23% of women had optimal sampling per-

formed at the primary visit. Since Denmark, until recently, has seen many years with a low gonorrhoea incidence, it may be that GPs have been unaware of national guidelines on gonorrhoea management. In support of this, we found that GPs were significantly more inclined to follow guidelines during recent higher-incidence years than in the initial part of the study period. Previous studies have shown that positive cultures from multiple sites are more common in homosexual men than in women and heterosexual men [7]. However, also female populations may present with a considerable incidence of non-genital gonorrhoea [16].

Failure of one-dose cephalosporin is a possibility for oropharyngeal gonorrhoea, and it remains an elusive infection that may contribute to the spread of gonococcal infection [14, 17, 18]. Very few infected patients report symptoms and these are non-specific and may be ignored. Conduct of TOC remains important in the management of oropharyngeal gonorrhoea. Our results suggest the possibility that even in treated patients, the pharynx may continue to represent a reservoir for transmission of gonorrhoea if TOC is not performed. In our study, TOC was not carried out for a significant proportion of patients, which is well known from other studies [15]. Patients' failure to attend the GP for TOC was the most common reason for this.

It has been reported that women have a concomitant chlamydial infection more often than men [7]. We observed this trend in our region, although the trend did not reach statistical significance. When sexually transmitted infection is suspected, it is important to examine for both chlamydial and gonorrhoeal disease. Azithromycin is normally recommended for *C. trachomatis* and it is commonly treated in general practice. Since this antimicrobial agent has some activity against *N. gonorrhoeae*, we cannot exclude that the number of gonorrhoea cases might have been higher if examination for gonorrhoea had been performed before therapy.

Since the introduction of antimicrobial therapy, *N. gonorrhoeae* has shown a considerable capacity for development of resistance. Penicillins are no longer active, and fluoroquinolone-resistance has increased dramatically in the past decade worldwide [6, 8, 9]. Previous data from another Danish region suggested an increase in ciprofloxacin-resistance [19]. In the RNJ the percentage of isolates resistant to ciprofloxacin varied through the period, but remained very high, and in most cases treatment therefore required intramuscular ceftriaxone. Due to the unpredictable susceptibility of gonorrhoeal isolates, the use of microscopy or polymerase chain reaction methods for diagnostics cannot stand alone since culture of the microorganism allows for resistance testing. High risk of acquiring quinolone-resistant gonorrhoea has formerly been related to sex abroad [5]. This

was not the case in the RNJ during the increase in cases in 2008-2009, and we conclude that resistant isolates are now established as endemic strains in our region. Our results stress the importance of surveillance to monitor trends in gonorrhoeal resistance so that timely changes to treatment recommendations can be made in response to changing epidemiology. Emerging resistance to ceftriaxone is reported [11], and susceptibility testing of all gonorrhoeal cases in Denmark is recommended since international spread of extensively drug-resistant gonococci is realistic and probably will occur.

In patients allergic to cephalosporins, treatment options are limited to azithromycin and maybe aminoglycosides. However, resistance to macrolides has been reported [20]. We observed successful therapy in two cases of gentamicin treatment.

The strengths of our study are the population-based cohort with a centralized diagnostic laboratory and the ability to report annual incidences and monitor the susceptibility to critical drugs used for treatment. The limitations of the study are the low frequency of sampling from non-genital sites, the lack of information on contract tracing and the limited information on travel history. Through the study period, the adherence to national guidelines for sampling increased, but it could be further improved. We observed no treatment failures, no isolates were resistant to cephalosporins. However, continuous monitoring of susceptibility is recommended as emerging resistance has been reported from several countries.

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**CONFLICTS OF INTEREST:** Disclosure forms provided by the authors are available with the full text of this article at [www.danmedj.dk](http://www.danmedj.dk).

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