

Susceptibility patterns in *Neisseria gonorrhoeae* in Nuuk, Greenland, 2015-2018: a short communication

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ABSTRACT

Antimicrobial resistance in *Neisseria gonorrhoeae* (GC) has made gonorrhoea control and treatment more complex globally. In Greenland, the incidence of gonorrhoea is high and there is a need for continued surveillance of antimicrobial susceptibility.

This study investigated gonococcal isolates obtained in Greenland's capital Nuuk between January 2015 and June 2018. Subsequent to collection, isolates were tested for ciprofloxacin and ceftriaxone susceptibility in order to monitor the resistance pattern among GC strains. 150 GC strains were isolated in Nuuk during the observation period (139 males, 93%; 11 females, 7%). All strains were fully susceptible to ceftriaxone. 49% of the GC strains were susceptible to ciprofloxacin. The median minimal inhibitory concentration (MIC) for ceftriaxone among GC strains resistant to ciprofloxacin was higher than among GC strains susceptible to ciprofloxacin. No differences in ciprofloxacin susceptibility and median MICs for ceftriaxone were observed by collection year. In conclusion no ceftriaxone resistance has been found in Nuuk to date. Continued easy access to diagnostics and treatment combined with increased and more systematic surveillance of antimicrobial susceptibility in Nuuk is recommended. Further, it is advisable to investigate the possibilities for intermittent sampling in Greenland outside of Nuuk, if obstacles in relation to sending sampling material to Nuuk can be bypassed.

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Introduction

Gonorrhoea and other sexually transmitted diseases (STDs) are highly prevalent in Greenland. Over the last years, Greenland has seen a rise in gonorrhoea rates [1]. In 2017, a total of 1216 infections were seen among 1085 different persons. This corresponds to 194 infected persons per 1000 persons (more than 30-fold higher than the incidence in Denmark) [2].

The highest incidence was seen in the age group 15–24 years of age, who made up 60% of all infected persons (message from Henrik Lyngbeck Hansen, Chief Medical Officer, National board of Health, Greenland; unreferenced). Rapid emergence and spread of antimicrobial resistance (AMR) in the causative agent *Neisseria gonorrhoeae* (GC) has been documented globally [3] as well as locally in Greenland [1,4].

Systematic surveillance to monitor susceptibility patterns of GC throughout the country of Greenland is not a regular feature in the national control of STDs. However, susceptibility has been surveyed continuously in the capital, Nuuk.

In the latest report from 2016, ciprofloxacin resistance was examined in a prospective cohort study with 102 gonococcal isolates obtained between March 2012 and February 2013. Further, an additional 18 isolates were characterised after introduction of a ciprofloxacin-resistant strain into Greenland in early 2014. During the study period (2012–2013) all isolates were fully susceptible to ciprofloxacin and ceftriaxone. However, the new ciprofloxacin resistant strain, detected in 2014, dominated the population, with 59% resistant isolates, within 6 months after its introduction [5]. Consequently, in 2014, it was decided to change therapy from the previously used ciprofloxacin regimen to the internationally recommended dual therapy with ceftriaxone (cephalosporin) 500 mg intramuscularly supplemented with 2 g of azithromycin orally, both as a single dose.

However, since then, no evaluation of neither ciprofloxacin nor ceftriaxone susceptibility has been performed.

Control and treatment of gonorrhoea has generally become more complex globally. The recent emergence of strains resistant to extended-spectrum cephalosporins such

as ceftriaxone is threatening the last available treatment options.

Thus, our objective was to estimate the current ciprofloxacin and ceftriaxone susceptibility among GC strains tested in Nuuk from January 2015 to May 2018.

Material and methods

On 1 January 2018, 55,877 people were living in Greenland and around 17,000 of them were living in the capital Nuuk.

Queen Ingrid Health Care Centre provides primary health care to all inhabitants in Nuuk. Testing for GC is free to anyone attending the health care centre.

In the study period, the initial test for GC was performed on a first-void urine sample. The urine was tested with a nucleic acid amplification test (NAAT) by strand displacement amplification (ProbeTec ET analysed on a Viper automated platform, Becton, Dickinson and Company, Sparks, Maryland, USA). The indications for NAATs performed in the study period were symptoms or sexual risk behaviour, partner notification, insertion of intrauterine device and pregnancy (including women undergoing induced abortion).

All male patients with a positive NAAT were offered GC culture test from the urethra using an eSwab® (Copan, Brescia, Italy). A few specimens were obtained from women having a gynaecological exam performed and a cervical swab collected. Due to limited resources, the testing strategy was primarily targeting men.

Specimens were cultured on chocolate-agar plates with antibiotics (SSI Diagnostica, Hillerød, Denmark) and ciprofloxacin and ceftriaxone susceptibility testing was performed with Etest (BioMérieux S.A., Marcy l'Etoile, France) on chocolate-agar plates without antibiotics. Strains with a minimal inhibitory concentration (MIC) for ciprofloxacin <0.032 mg/L were considered susceptible. Strains with an MIC for ceftriaxone <0.125 mg/L were considered susceptible.

Variables were described using medians and inter quartiles range (IQR). Medians among groups were compared using Mann-Whitney U Test (2 groups) or Kruskal-Wallis test. Proportions were compared using Fischer exact test. Linear trend test was used to test for trends among categories. A 2-sided p-value < 0.05 was used as level of

significance. Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 23.0 was used.

Ethics

The study complies with the Helsinki Declaration II and was approved by The Ethics Committee for Medical Research in Greenland (No. KVUG 2018–05) and the Agency for Health and Prevention in Greenland.

Results

A total of 150 GC strains were isolated in Nuuk during the study period from the beginning of 2015 to June 2018 (139 males, 93%; 11 females, 7%). The median age was 25 years. The anatomical site of specimen collection was solely urogenital.

All 150 GC strains were fully susceptible to ceftriaxone with MICs below 0.125 mg/L, indicating absence of ceftriaxone-resistant GC strains in Nuuk. No difference between males and females were observed concerning age (males 25 years; IQR 9, females 29 years; IQR 11) ($p = 0.444$), median MIC for ceftriaxone (males 0.006mg/L; IQR 0.01, females 0.008mg/L; IQR 0.01) ($p = 0.624$) or proportion of strains that were ciprofloxacin susceptible (males 50.4% (70/139), females 37.5% (3/11), $p = 0.211$). The proportion of GC strains susceptible to ciprofloxacin and the median MICs for ceftriaxone are shown in [Table 1](#). Among all 150 isolated strains of GC, 49% (73/150) were ciprofloxacin susceptible. The median MIC for ceftriaxone was 0.006mg/L and MIC₉₀ (the lowest concentration of ceftriaxone at which 90% of the isolates were inhibited) was 0.022 mg/L. No differences in ciprofloxacin susceptibility and median MICs for ceftriaxone were observed by collection year (see [Table 1](#)). The median MIC for ceftriaxone among GC strains resistant to ciprofloxacin was higher (0.0120mg/L; IQR 0.0095) than among GC strains susceptible to ciprofloxacin (0.002mg/L; IQR 0.001) ($p < 0.001$).

Discussion

This study documents that around half of the GC strains from Nuuk were resistant to ciprofloxacin. No rising trend in ceftriaxone MICs was observed over the study period and the continued absence of ceftriaxone-

Table 1. Proportion of GC strains susceptible to ciprofloxacin and median MICs for ceftriaxone by year.

Variable – Year	2015 n = 68	2016 n = 32	2017 n = 27	2018 n = 23	p	Total n = 150
Ciprofloxacin susceptible n (%)	30 (44)	24 (75)	9 (33)	10 (43)	0.616	73 (49)
MIC (mg/L) Ceftriaxone Median (IQR)	0.004 (0.010)	0.005 (0.014)	0.006 (0.010)	0.006 (0.010)	0.802	0.006 (0.010)

resistant GC in Nuuk was encouraging. A higher median MIC for ceftriaxone in the ciprofloxacin *resistant* strains compared to the ciprofloxacin susceptible strains was observed, most likely reflecting a few circulating GC clones as previously found in an earlier study from Nuuk where 2 dominating strains were identified [5]. In this study, all isolates before 2014 were fully susceptible to ciprofloxacin, azithromycin, spectinomycin, gentamicin and ceftriaxone. After strain typing, 2 dominating clones were found. The ST210 clone dominated before the introduction of ciprofloxacin resistance in Greenland in January 2014. However, the ciprofloxacin-resistant ST 2400 strain presented the largest cluster shortly after [5]. In the present study, azithromycin susceptibility testing was not attempted and no strain typing was performed. This is a weakness of the study, and future surveillance should include monitoring for azithromycin resistance, as azithromycin is part of the recommended first-line treatment in Greenland. Dual therapy with ceftriaxone and azithromycin is recommended in both European and American guidelines [6,7] as a strategy to delay development of ceftriaxone resistance, but azithromycin resistance is described in many countries, which might threaten this dual therapy in the longer term [8].

The continued monitoring with samples for culture in Nuuk over the last years has been highly relevant. Yet, surveillance coverage has been modest and the number of isolates obtained is low in comparison to the high number of infections. Men from Nuuk have primarily been tested between 2015 and 2018 and collection of samples has been somewhat random. To get a full overview of the current state, a more structured and systematic surveillance of gonorrhoea and antibiotic susceptibility is recommended. Isolates should be obtained from a larger group of people and surveillance should be increased in women. This would help support national treatment guidelines and public health interventions concerning gonorrhoea, which is urgently needed in Greenland.

Moreover, it would be relevant to include inhabitants from other areas of Greenland. However, currently this is not possible because of logistic challenges with transportation of specimens from the smaller cities/communities along the coast. As the current surveillance only takes place in Nuuk, we cannot rule out a possibility of ceftriaxone resistant strains spreading in the Greenlandic population.

In a global situation with multidrug-resistant gonorrhoea, ongoing AMR surveillance of GC is critical. Greenland has an extremely high incidence of gonorrhoea being >30-fold higher than that seen in Denmark [2]. Together with a high incidence of chlamydia [4], which is

treated with azithromycin 1 g single dose in cases of genitourinary infection, the selective pressure with macrolides is dramatic in the 15–35 years age group where the highest prevalence of STDs is found. Surveillance of macrolide resistance in GC should, therefore, be introduced immediately. One of the effects of the high consumption of azithromycin is also seen in *Mycoplasma genitalium*, where 100% of the known strains in Greenland carry macrolide resistance markers [9]. Although this STD is currently not diagnosed in Greenland, such findings would strongly argue for a change in treatment strategy for first-line treatment of chlamydia to doxycycline as it would eradicate 30–40% of the macrolide resistant *Mycoplasma genitalium* infections and diminish the macrolide selective pressure on GC. This would be in accordance with the European Guidelines for management of non-gonococcal urethritis [10].

Persistent focus on preventive measures is of utmost importance. Continued easy access to diagnostics and treatment combined with surveillance in Nuuk is recommended, but more resources should also be invested in primary prevention including a strong collaboration between health services, municipality, schools, young people in the community and their parents as well as increased partner tracing and education.

Disclosure statement

No potential conflict of interest was reported by the authors.

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