No evidence of reduced cephalosporin susceptibility of circulating strains of Neisseria gonorrhoeae in the Netherlands despite nearly a decade of recommending ceftriaxone monotherapy

Title

No evidence of reduced cephalosporin susceptibility of circulating strains of *N. gonorrhoeae* in the Netherlands despite nearly a decade of recommending ceftriaxone monotherapy

Brief title

Ceftriaxone monotherapy against gonorrhoea

Authors

Christophe Van Dijck MD[1, 2,*], Prof Chris Kenyon PhD[1, 3]

1. STI unit, Institute of Tropical Medicine Antwerp, Antwerp, Belgium
2. Laboratory of Medical Microbiology, University of Antwerp, Antwerp, Belgium
3. Division of Infectious Diseases and HIV Medicine, University of Cape Town, South Africa

*corresponding author: cvandijck@itg.be, Institute of Tropical Medicine Antwerp, Nationalestraat 155, 2000 Antwerp, Belgium, phone: +32 (0)3 247 07 86

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Gonorrhoea, antimicrobial resistance, therapy, Europe, guidelines

Due to increasing antimicrobial resistance (AMR), ceftriaxone is the only remaining single-dose antibiotic effective against *Neisseria gonorrhoeae.* [1] To preserve this treatment option, since 2012 guidelines have recommended combination therapy with azithromycin.[1] The rationale was that azithromycin would eradicate isolates with reduced ceftriaxone susceptibility and thereby prevent the emergence of ceftriaxone resistance.[1]. However, no randomized controlled trials (RCTs) have assessed if combination therapy is superior to monotherapy for the treatment of gonorrhoea in terms of efficacy or emergence of AMR. Meta-analyses have found no difference in efficacy between monotherapy and dual therapy. [2] In fact, increasing macrolide exposure may promote AMR acquisition. [3] These considerations have led some guidelines to change back to recommending ceftriaxone monotherapy for uncomplicated gonorrhoea and the 2020 European guidelines now include monotherapy as an alternative. [4–6]

Dutch guidelines are unusual in that, unlike the rest of Europe, they never recommended dual therapy; a single 500 mg intramuscular dose of ceftriaxone has been the preferred treatment for gonorrhoea since 2011.[7] This policy allowed us to test whether between 2012 and 2019, the use of ceftriaxone monotherapy in the Netherlands was associated with lower ceftriaxone susceptibility in circulating strains of *N. gonorrhoeae* as compared to countries were dual therapy was recommended.

We compared ceftriaxone, cefixime and azithromycin susceptibility of gonococcal isolates from the Netherlands with that of isolates from the remaining 26 European countries participating in Euro-GASP between 2012 and 2019.[8] For each antibiotic, we applied a mixed effects linear regression model to estimate the association between the isolates' logarithmically transformed minimum inhibitory concentration (MIC) and treatment policy in the country of collection (monotherapy in the Netherlands; dual therapy in the remaining countries). The model was adjusted for gender, mode of transmission, year of MIC reporting and country-level antibiotic consumption in the year before the isolate was collected. Antibiotic consumption data were derived from the European Surveillance of Antimicrobial Consumption Network, ESAC-Net.[9] To account for residual confounding and for the

longitudinal nature of the data, country of reporting was included as a random effect. Outcomes of the regression model were exponentiated to obtain odds ratios (OR) which indicate change in geometric mean MIC.

More than 20,000 isolates were included (Table 1, Supplementary Table S1). The United Kingdom, the Netherlands and Spain contributed 9.9%, 9.4% and 8.3% of all MIC values, respectively (Supplementary Figure S1). Antibiotic consumption in the Netherlands was among the lowest in Europe (Supplementary Figure S2). The monotherapy policy in the Netherlands was not associated with the geometric mean MIC for ceftriaxone (OR 0.46, 95% CI 0.12 – 1.77) or cefixime (OR 0.52, 95% CI 0.17 – 1.57), but was associated with a lower geometric mean MIC for azithromycin compared to other countries (OR 0.59, 95% CI 0.35 – 0.98). These findings suggest that nearly a decade of ceftriaxone monotherapy in the Netherlands was not associated with reduced cephalosporin susceptibility of circulating *N. gonorrhoeae* isolates.

There are limitations to our analysis, including those inherent to surveillance data, and the possibility that healthcare providers may not follow national treatment guidelines. In addition, our analysis may have been insensitive to the impact of recently circulating strains with reduced cephalosporin susceptibility.[10] In addition, note that the confidence intervals of the effect estimates are very wide, which is due to large variability in the data and indicates a large margin of error. The Dutch data contrast with those from China where a high prevalence of gonococci with reduced ceftriaxone susceptibility has been reported under ceftriaxone monotherapy.[11,12] Thus, at least in some settings, monotherapy may not be sufficient to prevent gonococcal ceftriaxone resistance. Nonetheless, the increasing prevalence of azithromycin resistance over the last decade in multiple countries raises questions as to whether dual therapy is causing more harm than benefit.

Ideally, future decisions about optimal therapy for gonorrhoea should be based on RCTs. Capturing differences in the risk of AMR between different therapies may prove challenging however, as the effect would operate at a population level and may be missed by individual-level studies such as RCTs.

Comparisons of bacterial susceptibilities of populations exposed to dual- vs. monotherapy may help detect this effect. Our analysis adds weight to the evidence that ceftriaxone monotherapy compared to dual therapy is not associated with increasing cephalosporin MICs.

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Authors' contributions

CK conceptualized the study, CK and CVD analysed the data, CVD drafted the manuscript, CK and CVD revised and finalized the manuscript.

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Author Disclosure Statement

All authors report no conflicts or competing interests to declare.

Availability of data

All data used in this study are publicly available from Euro-GASP and ESAC-NET.

Other

The results of this study were presented as an abstract and oral session at the 32nd European Congress of Clinical Microbiology and Infectious Diseases, Lisbon, April 23-26, 2022.

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Table 1: Associations between gonococcal minimum inhibitory concentration and gonococcal therapeutic policy (multivariate mixed-effects linear regression model).

	Azithromycin (n = 22,381 isolates from 27 countries)			**Cefixime** (n = 18,416 isolates from 26 countries*)			**Ceftriaxone** (n = 21,665 isolates from 26 countries*)		
Predictors	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P- value**
Recommended therapy									
dual therapy in other countries	Ref	-	-	Ref	-	-	Ref	-	-
monotherapy in NL	0.59	0.35 – 0.98	**0.042**	0.52	0.17 – 1.57	0.244	0.46	0.12 – 1.77	0.259
Year of reporting	1.05	1.04 – 1.06	**<0.001**	0.96	0.96 – 0.97	**<0.001**	0.94	0.94 – 0.95	**<0.001**
Country-level consumption (DID)									
macrolides	0.99	0.96 – 1.03	0.766	-	-	-	-	-	-
cephalosporins	-	-	-	0.80	0.77 – 0.84	**<0.001**	0.81	0.77 – 0.86	**<0.001**
Gender									
male	Ref	-	-	Ref	-	-	Ref	-	-
female	0.85	0.81 – 0.89	**<0.001**	0.92	0.88 – 0.95	**<0.001**	0.94	0.90 – 0.98	**0.003**
Unknown	1.10	0.93 – 1.30	0.254	0.82	0.71 – 0.94	**0.004**	1.09	0.92 – 1.29	0.309
Transmission mode									
hetero	Ref	-	-	Ref	-	-	Ref	-	-
MSM	1.32	1.26 – 1.38	**<0.001**	0.93	0.90 – 0.97	**0.001**	1.04	0.99 – 1.09	0.097
unknown	1.10	1.05 – 1.15	**<0.001**	1.00	0.96 – 1.05	0.828	0.95	0.91 – 1.00	**0.036**
Test method									
agar dilution	Ref	-	-	Ref	-	-	Ref	-	**-**
Etest	1.01	0.92 – 1.10	0.829	1.09	0.99 – 1.20	0.074	0.60	0.55 – 0.67	**<0.001**

DID = defined daily doses per 1000 individuals per day; MSM = men who have sex with men; NL = Netherlands

*no MIC values for ceftriaxone and cefixime were available from 1 country (Finland)

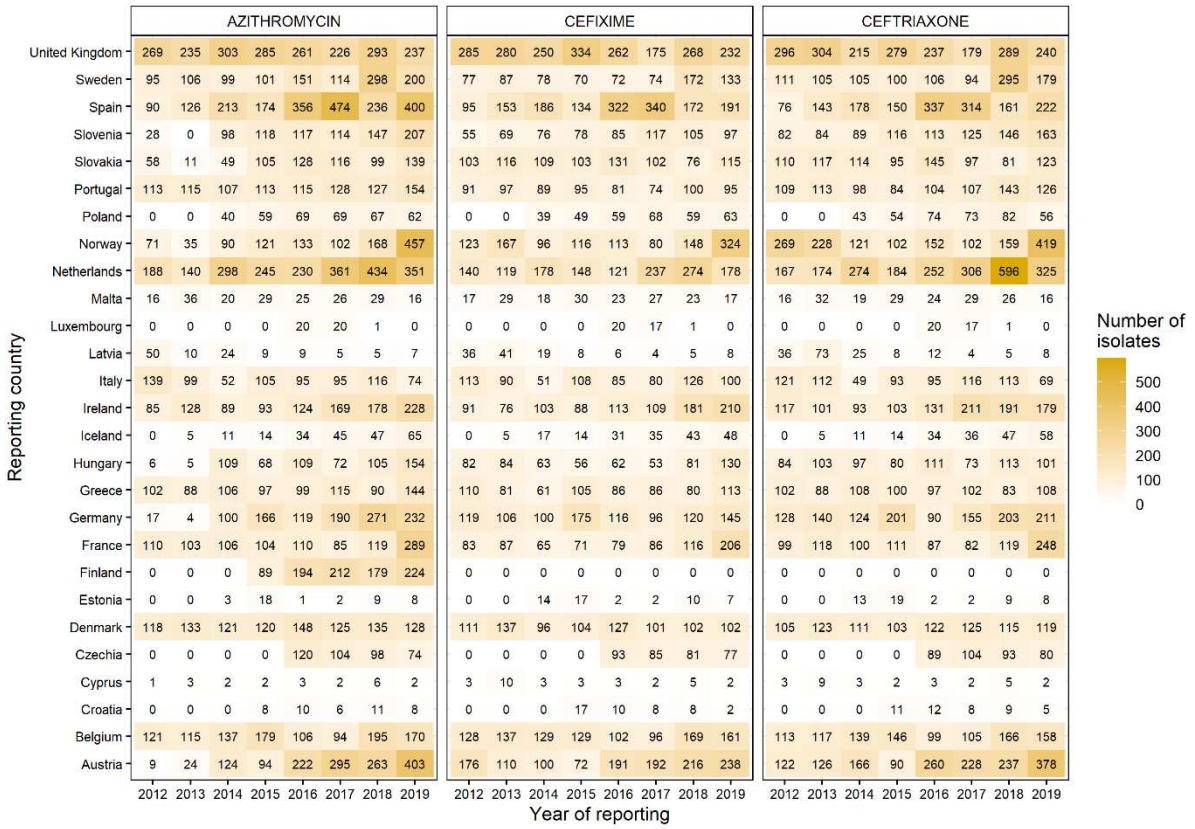
Supplementary Tables

Supplementary Table S1: Characteristics of isolates with reported MIC for azithromycin (data from Euro-GASP).

		Monotherapy (Netherlands) (N=2,247)	Dual therapy (Other countries) (N=20,410)	Chi square P-value
Gender	v			
Male		1,901 (84.6%)	16,588 (81.3%)	<0.001
Female		308 (13.7%)	3,666 (18.0%)	
Unknown		38 (1.7%)	156 (0.8%)	
Transmission mode				
Unknown/other		39 (1.7%)	9,292 (45.5%)	<0.001
Hetero		557 (24.8%)	6,369 (31.2%)	
MSM		1,651 (73.5%)	4,749 (23.3%)	
Test method				
Etest		2,247 (100%)	17,173 (84.1%)	<0.001
Agar dilution		0 (0%)	3,237 (15.9%)	

Supplementary Figures

Supplementary Figure S1: Number of isolates, by country and year of reporting (data from Euro-GASP). The number of isolates may differ per antibiotic for the same country as not every isolate was tested for all three antibiotics in every country.



Supplementary Figure S2: Antibiotic consumption, by country and year of reporting (data from ESAC-Net). DDD = defined daily doses. Crossed cells represent absence of reported data.