

This item is the archived peer-reviewed author-version of:

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

Reference:

Van Dijck Christophe, Kenyon Chris.- No evidence of reduced cephalosporin susceptibility of circulating strains of Neisseria gonorrhoeae in the Netherlands despite nearly a decade of recommending ceftriaxone monotherapy Sexually transmitted infections - ISSN 1472-3263 - London, Bmj publishing group, 99:3(2023), p. 213-214 Full text (Publisher's DOI): https://doi.org/10.1136/SEXTRANS-2022-055603 To cite this reference: https://hdl.handle.net/10067/1927440151162165141

uantwerpen.be

Institutional repository IRUA

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

Keywords

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.

3

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.

Acknowledgements

We would like to thank Euro-GASP and ESAC-Net for providing us with the data used in this analysis.

Authors' contributions

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

Funding information

No funding

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.

References

- Bignell C, Unemo M. 2012 European guideline on the diagnosis and treatment of gonorrhoea in adults. *Int J STD AIDS* 2013;**24**:85–92. doi:10.1177/0956462412472837
- Lo FWY, Kong FYS, Hocking JS. Treatment efficacy for rectal Neisseria gonorrhoeae: A systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother* 2021;**76**:3111–24. doi:10.1093/jac/dkab315
- 3 Kenyon C. Dual azithromycin/ceftriaxone therapy for gonorrhoea in PrEP cohorts results in levels of macrolide consumption that exceed resistance thresholds by up to 7-fold. *J Infect Dis*
- 4 Fifer H, Saunders J, Soni S, *et al.* 2018 UK national guideline for the management of infection with Neisseria gonorrhoeae. *Int J STD AIDS* 2020;**31**:4–15. doi:10.1177/0956462419886775
- 5 Cyr SS, Barbee L, Workowski KA, *et al.* Update to CDC 's Treatment Guidelines for Gonococcal Infection, 2020. *Morb Mortal Wkly Rep* 2020;**69**:1911–6.
- Unemo M, Ross JDC, Serwin AB, *et al.* 2020 European guideline for the diagnosis and treatment of gonorrhoea in adults. *Int J STD AIDS* Published Online First: 2020.
 doi:10.1177/0956462420949126
- Nederlandse Vereniging voor Dermatologie en Venereologie. Multidisciplinaire Richtlijn
 Seksueel Overdraagbare Aandoeningen voor de 2e Lijn. 2012;:153.
- 8 Spiteri G, Cole M, Unemo M, *et al.* The European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP)-a sentinel approach in the European Union (EU)/European Economic Area (EEA). *Sex Transm Infect* 2013;**89**:16–9. doi:10.1136/sextrans-2013-051117
- 9 ESAC. European Surveillance of Antimicrobial Consumption Program, Antimicrobial consumption database (ESAC-Net). https://www.ecdc.europa.eu/en/antimicrobial-consumption/surveillance-and-disease-data/database (accessed 27 Jul 2021).

- 10 De Korne-Elenbaas J, Bruisten SM, De Vries HJC, *et al.* Emergence of a Neisseria gonorrhoeae clone with reduced cephalosporin susceptibility between 2014 and 2019 in Amsterdam, the Netherlands, revealed by genomic population analysis. *J Antimicrob Chemother* 2021;**76**:1759–68. doi:10.1093/jac/dkab082
- 11 Yan J, Xue J, Chen Y, *et al.* Increasing prevalence of Neisseria gonorrhoeae with decreased susceptibility to ceftriaxone and resistance to azithromycin in Hangzhou, China (2015-17). *J Antimicrob Chemother* 2019;**74**:29–37. doi:10.1093/jac/dky412
- Han Y, Yin Y, Dai X, et al. Widespread Use of High-dose Ceftriaxone Therapy for
 Uncomplicated Gonorrhea Without Reported Ceftriaxone Treatment Failure: Results from 5
 Years of Multicenter Surveillance Data in China. *Clin Infect Dis* 2020;**70**:99–105.
 doi:10.1093/cid/ciz170

Table 1: Associations between gonococcal minimum inhibitory concentration and gonococcal therapeutic policy

	Azithro	omycin		Cefixin	ne		Ceftriaxone						
	(n =	22,381 isolates	from 27	(n =	18,416 isolates	from 26	(n = 21,665 isolates from 2						
	countr	ies)		countr	ies*)		countries*)						
Predictors	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P- value				
Recommended therapy													
dual therapy in other	Ref	-	-	Ref	-	-	Ref	-	-				
countries													
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				

(multivariate mixed-effects linear regression model).

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

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

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.

				AZ	ITHR	OMY	CIN						CEF	XIME							CI	FTR	AXO	NE					
	United Kingdom -	269	235	303	285	261	226	293	237	285	280	250	334	262	175	268	232	:	296	304	215	279	237	179	289	240			
	Sweden -	95	106	99	101	151	114	298	200	77	87	78	70	72	74	172	133		111	105	105	100	106	94	295	179			
	Spain -	90	126	213	174	356	474	236	400	95	153	186	134	322	340	172	191		76	143	178	150	337	314	161	222			
	Slovenia -	28	0	98	118	117	114	147	207	55	69	76	78	85	117	105	97	1	82	84	89	116	113	125	146	163			
	Slovakia -	58	11	49	105	128	116	99	139	103	116	109	103	131	102	76	115		110	117	114	95	145	97	81	123			
	Portugal -	113	115	107	113	115	128	127	154	91	97	89	95	81	74	100	95		109	113	98	84	104	107	143	126			
	Poland -	0	0	40	59	69	69	67	62	0	0	39	49	59	68	59	63		0	0	43	54	74	73	82	56			
	Norway -	71	35	90	121	133	102	168	457	123	167	96	116	113	80	148	324	-	269	228	121	102	152	102	159	419			
	Netherlands -	188	140	298	245	230	361	434	351	140	119	178	148	121	237	274	178		167	174	274	184	252	306	596	325			
	Malta -	16	36	20	29	25	26	29	16	17	29	18	30	23	27	23	17		16	32	19	29	24	29	26	16			
>	Luxembourg -	0	0	0	0	20	20	1	0	0	0	0	0	20	17	1	0		0	0	0	0	20	17	1	0		umbe	
Reporting country	Latvia -	50	10	24	9	9	5	5	7	36	41	19	8	6	4	5	8		36	73	25	8	12	4	5	8	13	Jates	,
COL	Italy -	139	99	52	105	95	95	116	74	113	90	51	108	85	80	126	100		121	112	49	93	95	116	113	69		500	С
ing	Ireland -	85	128	89	93	124	169	178	228	91	76	103	88	113	109	181	210		117	101	93	103	131	211	191	179		400	
out	Iceland -	0	5	11	14	34	45	47	65	0	5	17	14	31	35	43	48		0	5	11	14	34	36	47	58		300	
Rep	Hungary -	6	5	109	68	109	72	105	154	82	84	63	56	62	53	81	130		84	103	97	80	111	73	113	101		200	
_	Greece -	102	88	106	97	99	115	90	144	110	81	61	105	86	86	80	113		102	88	108	100	97	102	83	108		100	1
	Germany -	17	4	100	166	119	190	271	232	119	106	100	175	116	96	120	145		128	140	124	201	90	155	203	211		U	
	France -	110	103	106	104	110	85	119	289	83	87	65	71	79	86	116	206		99	118	100	111	87	82	119	248			
	Finland -	0	0	0	89	194	212	179	224	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0			
	Estonia -	0	0	3	18	1	2	9	8	0	0	14	17	2	2	10	7		0	0	13	19	2	2	9	8			
	Denmark -	118	133	121	120	148	125	135	128	111	137	96	104	127	101	102	102	1	105	123	111	103	122	125	115	119			
	Czechia -	0	0	0	0	120	104	98	74	0	0	0	0	93	85	81	77		0	0	0	0	89	104	93	80			
	Cyprus -	1	3	2	2	3	2	6	2	3	10	3	3	3	2	5	2		3	9	3	2	3	2	5	2			
	Croatia -	0	0	0	8	10	6	11	8	0	0	0	17	10	8	8	2		0	0	0	11	12	8	9	5			
	Belgium -	121	115	137	179	106	94	195	170	128	137	129	129	102	96	169	161	1	113	117	139	146	99	105	166	158			
	Austria -	9	24	124	94	222	295	263	403	176	110	100	72	191	192	216	238		122	126	166	90	260	228	237	378			
		2012	2013	2014	2015	2016	2017	2018	2019	2012	2013			2016 repo		2018	2019	2	2012	2013	2014	2015	2016	2017	2018	2019			

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.

		J01F M	acrolide	s, Lincos	samides	Strepto	gramins		J01D Other beta-lactams antibacterials									
United Kingdom -	2.81	3.1	3.2	3.24	3.1	3.02	2.9	2.64	0.42	0.35	0.34	0.32	0.28	0.25	0.24	0.22		
Sweden -	0.61	0.63	0.62	0.61	0.6	0.54	0.54	0.5	0.18	0.18	0.16	0.15	0.14	0.14	0.08	0.0		
Spain -	2.06	1.88	1.94	2.04	2.25	3.19	3.07	3.05	1.53	1.44	1.57	1.64	1.64	2.24	2.27	2.35		
Slovenia -	1.95	1.79	1.78	1.76	1.85	1.59	1.68	1.78	0.33	0.3	0.3	0.28	0.31	0.33	0.37	0.32		
Slovakia -	5.76	4.91	5.89	5.56	6.2	5.44	4.68	4.72	3.88	3.49	4.51	4.37	4.71	4.62	4.58	6.2		
Portugal -	3.39	3.21	2.74	2.79	3.06	3.09	2.44	2.68	1.65	1.55	1.43	1.44	1.56	1.54	1.64	1.6		
Poland -			3.89	3.79	4.6	4.19	4.46	6.01	1		2.5	2.37	2.87	2.75	3.99	3.0		
Norway -	2	2	1.69	1.47	1.31	1.15	1.01	0.89	0.12	0.11	0.11	0.09	0.08	0.07	0.06	0.0		
Netherlands -	1.5	1.5	1.39	1.35	1.39	1.37	1.38	1.45	0.04	0.04	0.04	0.04	0.04	0.03	0.03	0.0		
Malta -	3.67	3.7	3.96	3.77	4	3.91	4.46	4.53	5.68	5.27	5.52	4.57	4.11	3.57	3.12	2.7		
Luxembourg -					3.64	3.85	5.5						3.46	3.38	2.36			
Latvia - Italy - Ireland - Iceland - Hungary -	1.38	1.53	1.73	1.61	1.83	1.81	1.97	2.04	0.5	0.47	0.52	0.48	0.52	0.57	0.66	0.6		
Italy -	4.98	4.69	4.8	4.66	4.61	4.34	3.75	3.87	2.53	2.36	2.48	2.34	2.33	2.26	1.94	2.0		
lreland -	4.17	4.16	4.38	4.15	4.2	4.38	4.19	4.08	1.21	1.24	1.36	1.1	1.16	1.17	1.08	1.1		
Iceland -		1.66	1.71	1.56	1.71	1.69	1.61	1.57		0.69	0.76	0.46	0.46	0.51	0.61	0.5		
Hungary -	3.05	2.73	2.82	3.13	3.3	2.82	2.8	2.82	1.91	1.77	1.81	1.87	1.98	2.06	2.1	2.1		
Greece -	9.54	7.81	7.22	7.88	7.5	6.07	6.98	6.35	7.72	6.56	7.4	7.29	7.53	7.43	7.7	7.8		
Germany -	2.29	2.68	2.8	2.48	2.4	2.27	2.14	1.94	2.72	2.82	3.22	3.01	3.11	3.03	2.81	2.4		
France -	3.84	3.7	3.5	3.01	3.23	2.97	3.04	2.89	2.55	2.39	2.25	2.05	2.12	1.94	1.6	1.4		
Finland -				1.17	1.03	0.91	0.75	0.71				2.25	2.1	2.05	1.94	1.9		
Estonia -			2.48	2.4	2.45	2.27	2.26	2.33			1.1	1.14	1.22	1.16	1.18	1.1		
Denmark -	2.66	2.25	1.84	1.84	1.84	1.8	1.62	1.48	0.05	0.03	0.03	0.03	0.03	0.03	0.03	0.0		
Czechia -					3.98							_	2.21		-			
Cyprus -	3.11	2.92	2.67	2.46	3.27	2.79	2.89	3.07	6.06	5.36	4.85	4.47	5.25	5.17	5.81	5.9		
Croatia -				2.91	3.1	2.71	2.75	2.83				2.81	2.74	2.49	2.47	2.5		
Belgium -	3.18	3.4	3.34	3.4	3.63	3.62	3.41	3.57	1.52	1.53	1.53	1.42	1.44	1.32	1.17	1.2		
Austria -	3.39	3.19	3.59	3.04	3.06	2.74	2.81	2.27	1.66	1.58	1.95	1.48	1.44	1.41	1.51	1.4		
_	2011	2012	2013	2014	2015	2016	2017	2018 (ear of	2011 reportin	2012 a	2013	2014	2015	2016	2017	201		

DDD per 1000 individuals per day

> 5.0 2.5