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Original article

Country-level association between antimicrobial consumption and *resistance in Neisseria meningitidis:* An ecological study

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ABSTRACT

Background: It is unclear what is responsible for the large variations in the prevalence of meningococcal resistance to cephalosporins and quinolones.
Methods: We used mixed-effects linear regression to assess if country-level prevalence of reduced susceptibility to cefotaxime and ciprofloxacin was associated with the population-level consumption of cephalosporins and quinolones in 13 European countries.
Results: Positive correlations were found between the prevalence of reduced susceptibility to ciprofloxacin and the consumption of quinolones (coef. 0.16, 95% CI 0.05–0.27; P = 0.003). The same positive association was found for cefotaxime/cephalosporins (coef. 0.1, 95% CI 0.04–0.15; P = 0.001).
Conclusions: Meningococcal reduced susceptibility to cefotaxime and ciprofloxacin is linked to homologous class antimicrobial consumption. This finding provides additional motivation for strengthening antimicrobial stewardship programs.

Background

There are striking variations in the prevalence of antimicrobial resistance (AMR) in *Neisseria meningitidis*. Surveillance studies in countries such as the United States and Sweden have reported a prevalence of resistance to quinolones and cephalosporins of close to zero [1,2]. In contrast, a survey of 198 isolates in Shanghai found that 68% were resistant to ciprofloxacin [3]. Although based on smaller sample sizes, similar results have been reported from India [4]. Considerable variation in the prevalence of reduced susceptibility to penicillin has also been noted between European countries [1,2]. For example, in two studies using similar methodologies, the prevalence of reduced susceptibility to penicillin varied between 8.6% in Sweden in 2008 and 41% in Belgium in 2010 [2,5]. More recently, high level resistance to cefotaxime has been reported [6].

Understanding the drivers of this AMR is important to prevent the further emergence of resistance. In this paper, we test the bystander-selection-hypothesis – the hypothesis that population level consumption of antimicrobials can influence the prevalence of AMR [7]. This theory is based on the observation that *N. meningitidis* is asymptomatic for most of the time it circulates in a population [1,8]. This means that antibiotics used for any indications could select for AMR in *N. meningitidis* (bystander selection) [7]. Previous studies have found that the country-level prevalence of cephalosporin, macrolide and quinolone resistance in *N. gonorrhoeae* is positively associated with the volume of homologous class antimicrobial consumption [9–11]. This association was found in both a global study and a study limited to European countries where there is considerable variation in the intensity of antimicrobial consumption [10,11]. Whilst this association has not been tested for *N. meningitidis*, a number of studies (but not all) have found that high level exposure to antimicrobials in mass meningococcal treatment or chemoprophylaxis campaigns is associated with the emergence of AMR [12–14].

We use two open access datasets to assess if there is a country-level association between the consumption of quinolones and cephalosporins and the time-lagged prevalence of resistance to these antimicrobial classes in European countries.

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Table 1
Variation in antimicrobial consumption, decreased susceptibility and resistance to cephalosporins, quinolones in *N. meningitidis* in 13 European Countries. Values reported as country medians of all the years with available data.

	Antimicrobial consumption (DID)			Decreased susceptibility (%)			Antimicrobial resistance (%)	
	Cephalosporins	Quinolones	N	Cefotaxime	N	Ciprofloxacin	Cefotaxime	Ciprofloxacin
Belgium	2.19	2.51	1	0	10	33.3	0	0
Czech Republic	1.365	1.1	252	0	13	21.4	0	0
France	2.92	1.88	90	42.9	104	19.5	0	0
Germany	1.59	1.25	253	6.1	288	0	0	0
Greece	7.4	2.36	67	35.7	67	53.8	0	0
Ireland	1.64	0.855	101	16.7	110	2.5	0	0
Italy	2.77	3.24	1	0	49	0	0	0
Malta	4.9	2.01	.	.	94	27.5	.	0
Poland	2.3	1.18	905	19.2	951	2.2	0	0
Portugal	1.99	2.98	9	100	121	42.9	0	0
Slovenia	0.52	1.11	265	0	265	0	0	0
Spain	1.81	2.29	46	0	53	16.7	0	0
Sweden	0.34	0.92	39	0	156	0	0	0

Notes: DID - number of defined daily doses per 1000 inhabitants; Decreased susceptibility and antimicrobial resistance are reported as percentages. The thresholds used to define antimicrobial resistance and reduced susceptibility are provided in the methods section. N – the number of isolates with antimicrobial susceptibility data available per country for cefotaxime or ciprofloxacin

Methods

Data

Antimicrobial consumption data

National population-level antimicrobial drug consumption data were obtained from the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) [15,16]. ESAC-Net provides open access to the data it collects on antimicrobial use in ambulatory care and hospital care in 30 European countries [15,16]. ESAC-Net reports antimicrobial consumption as the number of defined daily doses (DDD) per 1000 inhabitants (DID) following the World Health Organization (WHO) guidelines [16–18]. One DDD is defined as the average maintenance dose per day for a drug used in its main indication for adults [17]. Data provided by ESAC have been shown to be accurate and to correlate closely with those produced by other methodologies [16]. In our study, we used the total country-specific antimicrobial drug use in ambulatory care broken down into the following major antimicrobial classes: J01MA/quinolones and J01D/other β-lactam antimicrobial agents (cephalosporins, monobactams and carbapenems; we refer to this class as cephalosporins). We focused on quinolones and cephalosporins because of their importance in the current meningococcal treatment and chemoprophylaxis regimens [19]. Data were available from 1997 to 2018. All consumption figures are reported as DID.

Antimicrobial Resistance Data

The AMR data was calculated from the PubMLST dataset (STable 2). PubMLST is a collection of open-access, curated databases that integrate sequence data with metadata such as antimicrobial susceptibility data for over 100 bacterial species [20]. The dataset contains 64,458 isolates of *N. meningitidis* from both symptomatic and asymptomatic infections. Antimicrobial susceptibility data is, however, only available for only a fraction of these. We used data for ciprofloxacin (n = 3237), the only quinolone with susceptibility data was ciprofloxacin, and cefotaxime (n = 2551), the extended spectrum cephalosporin with the most data available.

We used this data to calculate the prevalence of resistance to cefotaxime and ciprofloxacin per country and year. For each antimicrobial, we calculated the percent of isolates that were resistant per country per year.

EUCAST (v11.0) uses the following minimum inhibitory concentration (MIC) breakpoints to define meningococcal antimicrobial resistance: cefotaxime: > 0.125 mg/L, ciprofloxacin: > 0.03 mg/L (https://www.eucast.org/clinical_breakpoints/).

Only a limited number of isolates in Europe are resistant according to these breakpoints (Table 1). To be able to detect more subtle effects of antimicrobial consumption on AMR, we used lower breakpoints to define decreased susceptibility: cefotaxime: > 0.008 mg/L, ciprofloxacin: > 0.008 mg/L [21]. We used these breakpoints to calculate the proportion of isolates from each country and year with decreased susceptibility to cefotaxime and ciprofloxacin. Datapoints with only data from a single isolate were dropped from the analysis.

As a sensitivity analysis, we repeated the analyses using the geometric mean MIC per country and year for cefotaxime and ciprofloxacin as outcome variables.

Analyses

Associations between decreased susceptibility in N. meningitidis and antimicrobial consumption

For each antibiotic class, mixed effects linear regression was used to assess the association between the decreased susceptibility in *N. meningitidis* and antimicrobial consumption.

The following mixed effects linear model was used:

(*N·meningitidis*_resistance-to-X in year Y and country C) ~ (*Consumption of* X in year Y-1 and country C) + (random intercept for country C) + intercept + error

We did not control for genogroup, sample type or asymptomatic versus symptomatic infection as multivariable mixed effects linear regression with country as a random intercept revealed that these factors were not significantly associated with ciprofloxacin or cefotaxime MICs (STable 2).

The statistical analyses were performed in Stata 16.0. A P-value of < 0.05 was regarded as significant.

Results

Antimicrobial consumption data was available from 30 countries, but antimicrobial susceptibility data was only available for 13 of these countries (Table 2). There were large variations in the median consumption of cephalosporins and quinolones between these 13 countries (cephalosporins - median 2.0 [IQR1.6 - 2.8; range 0.34 – 7.4], quinolones - median 1.9 [IQR 1.1 – 2.4; range 0.9 – 3.2]; Table 2; SFig. 1). Appreciable differences in the prevalence of reduced susceptibility to cefotaxime and ciprofloxacin were also evident (cefotaxime – median 11% [IQR 0–36%]; ciprofloxacin – median 17% [IQR 0–28%].

Table 2
Mixed-Effects Linear Regression Analyses of the relationship between the consumption of cephalosporins/quinolones and reduced susceptibility to cefotaxime/ciprofloxacin in *N. meningitidis* in in 13 European countries.

	Reduced susceptibility		Geometric mean	
	Coeff. (95% CI)	P-value	Coeff. (95% CI)	P-value
Cefotaxime	0.096 (0.039–0.153)	0.001	0.002 (0.001–0.004)	0.002
Ciprofloxacin	0.162 (0.054–0.269)	0.003	0.002 (−0.003 to 0.008)	0.348

Correlation between reduced antimicrobial susceptibility and consumption

Mixed-effects linear regression analyses, with a random intercept for the country, revealed positive correlations between the prevalence of reduced susceptibility to ciprofloxacin and the consumption of quinolones (coef. 0.16, 95% CI 0.05–0.27; P = 0.003). The same positive association was found for cefotaxime/cephalosporins (coef. 0.1, 95% CI 0.04–0.15; P = 0.001; Table 2).

Sensitivity analysis

A positive association was found between antimicrobial consumption and geometric mean MIC and the consumption of cephalosporins (coef. 0.002, 95% CI 0.0008–0.0037; P = 0.002) but not quinolones (Table 2).

Discussion

We found that for both cephalosporins and quinolones, the prevalence of reduced susceptibility in *N. meningitidis* was positively associated with the population level consumption of these antimicrobials. These results add *N. meningitidis* to a long list of bacterial species where population level consumption of antimicrobials has been linked to AMR. As such, they provide further motivation for high consumption populations to improve antimicrobial stewardship to prevent the further emergence and spread of antimicrobial resistance.

There are two main, non-exclusive pathways through which population-level antimicrobial consumption could select for reduced susceptibility in *N. meningitidis*. In the direct pathway, asymptomatic *N. meningitidis* colonization would come under direct selection pressure for AMR when antimicrobial consumption in a particular population exceeded a certain threshold. In the indirect pathway, intense antimicrobial consumption would select for AMR commensal *Neisseria* species, which could in turn pass the resistance conferring DNA to *N. meningitidis* via transformation [22]. A phylogenetic analysis from a large collection of isolates in Shanghai established that transformation from commensal *Neisseria* spp. was responsible for the majority of quinolone resistance in *N. meningitidis* [3]. Transformation of sections of *penA* from commensal *Neisseria* spp. has likewise played an important role in the genesis of meningococcal resistance to cephalosporins [21,23,24]. It is plausible that both pathways could operate in high consumption populations.

There are a number of important limitations to this analysis. The pubMLST data are not based on representative samples of each country included. Furthermore, the antimicrobial susceptibility of isolates was not assessed by a uniform method or performed in the same laboratory. The number of isolates with available MIC data was low for a number of the countries. These factors would be expected to operate as misclassification biases which typically result in a bias towards the null hypothesis [25]. This would be expected to reduce the statistical strength of any association found. The prevalence of different genogroups is known to vary between countries and certain studies have found that the proportion of isolates with AMR varies between different genogroups [1,26]. We did not control for national differences in the prevalence of genogroups as we found that genogroup was not associated with ciprofloxacin or cefotaxime MIC (STable 1). Our measure of antimicrobial consumption was based on ESAC data whose consumption estimates are very similar to those produced by different methodologies [27,28]. Our analysis was limited to European countries. Finally, we did not assess the effect of antimicrobial consumption on the prevalence of AMR but only on reduced susceptibility to cefotaxime and ciprofloxacin.

These limitations notwithstanding, our findings provide guidance for populations with a high prevalence of meningococcal antimicrobial resistance. Populations such as those of Shanghai, where the prevalence of ciprofloxacin resistance has reached 66% may benefit from strengthening antimicrobial stewardship campaigns in the general populations [3]. Future studies could evaluate if there are population-level thresholds for inducing AMR and, if so if consumption in a particular age or other demographic groups plays a disproportionately large effect on AMR [29].

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CRediT authorship contribution statement

CK, NG & SMB conceptualized the study. CK, NG & SMB were responsible for the acquisition, analysis and interpretation of data. All authors read and approved the final draft.

Consent for publication

Not applicable.

Data availability

The data we used is publicly available from: https://pubmlst.org/ .https://www.ecdc.europa.eu/en/antimicrobial-consumption/surveillance-and-disease-data/database.

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Competing interests

None to declare. All the authors declare that they have no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2022.01.012.

References

[1] Harcourt BH, Anderson RD, Wu HM, Cohn AC, MacNeil JR, Taylor TH. Population-based surveillance of Neisseria meningitidis antimicrobial resistance in the United States. Open Forum Infect Dis 2015;2(3):ofv117.

[2] Hedberg ST, Olcén P, Fredlund H, Unemo M. Antibiotic susceptibility of invasive Neisseria meningitidis isolates from 1995 to 2008 in Sweden – the meningococcal population remains susceptible. Scand J Infect Dis 2010;42(1):61–4.

[3] Chen ML, Zhang C, Zhang X, Chen M. Meningococcal quinolone resistance originated from several commensal neisseria species. Antimicrob Agents Chemother 2020;64(2). doi: ARTN e01494-19 /AAC.01494-19. PubMed PMID: WOS:000509748200005.

[4] Singhal S, Purnapatre KP, Kalia V, Dube S, Nair D, Deb M, et al. Ciprofloxacin-resistant neisseria meningitidis, Delhi, India. Emerg Infect Dis 2007;13(10):1614–6.

[5] Bertrand S, Carion F, Wintjens R, Mathys V, Vanhoof R. Evolutionary changes in antimicrobial resistance of invasive Neisseria meningitidis isolates in Belgium from 2000 to 2010: increasing prevalence of penicillin nonsusceptibility. Antimicrob Agents Chemother 2012;56(5):2268–72.

[6] World Health Organization. Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report. WHO, 2020. WHO Geneva, Switzerland; 2020.

[7] Tedijanto C, Olesen SW, Grad YH, Lipsitch M. Estimating the proportion of bystander selection for antibiotic resistance among potentially pathogenic bacterial flora. Proc Natl Acad Sci USA 2018;115(51):E11988–95. https://doi.org/10.1073/pnas.1810840115

[8] Jafri RZ, Ali A, Messonnier NE, Tevi-Benissan C, Durrheim D, Eskola J, et al. Global epidemiology of invasive meningococcal disease. Popul Health Metr 2013;11(1):1–9.

[9] Olesen SW, Torrone EA, Papp JR, Kirkcaldy RD, Lipsitch M, Grad YH. Azithromycin susceptibility among neisseria gonorrhoeae isolates and seasonal macrolide use. J Infect Dis 2019;219(4):619–23. https://doi.org/10.1093/infdis/jiy551

[10] Kenyon C, Buyze J, Spiteri G, Cole M, Unemo M. Population-level antimicrobial consumption is associated with decreased antimicrobial susceptibility in Neisseria gonorrhoeae in 24 European countries: an ecological analysis. J Infect Dis 2020;221(7):1107–16.

[11] Kenyon C, Buyze J, Wi T. Antimicrobial consumption and susceptibility of Neisseria gonorrhoeae: a global ecological analysis. Front Med 2018;5:329.

[12] McNamara LA, MacNeil JR, Cohn AC, Stephens DS. Mass chemoprophylaxis for control of outbreaks of meningococcal disease. Lancet Infect Dis 2018;18(9):E272–81. https://doi.org/10.1016/S1473-3099(18)30124-5. PubMed PMID: WOS:000442523800002.

[13] Millar JW, Siess EE, Feldman HA, Silverman C, Frank P. In vivo and in vitro resistance to sulfadiazine in strains of Neisseria meningitidis. JAMA 1963;186(2):139–41.

[14] Pearce MC, Sheridan JW, Pearce MC, Jones DM, Lawrence GW, Murphy DM, Masutti B, McCosker C, Douglas V, George D, O'Keefe A, Young F, Thomson M, Gorman B, Hansman D, Hill PS. Control of group C meningococcal disease in Australian aboriginal children by mass rifampicin chemoprophylaxis and vaccination. Lancet 1995;346(8966):20–3.

[15] European Centre for Disease Prevention and Control. Antimicrobial consumption - Annual Epidemiological Report for 2015. Stockholm: ECDC, 2018.

[16] Vander Stichele RH, Elseviers MM, Ferech M, Blot S, Goossens H, Group EP. European surveillance of antimicrobial consumption (ESAC): data collection performance and methodological approach. Br J Clin Pharmacol 2004;58(4):419–28. https://doi.org/10.1111/j.1365-2125.2004.02164.x

[17] World Health Organization. The anatomical therapeutic chemical classification system with defined daily doses (ATC/DDD). Norway: WHO, 2004. 2008.

[18] Coenen S, Gielen B, Blommaert A, Beutels P, Hens N, Goossens H. Appropriate international measures for outpatient antibiotic prescribing and consumption: recommendations from a national data comparison of different measures. J Antimicrob Chemother 2014;69(2):529–34. https://doi.org/10.1093/jac/dkt385

[19] van de Beek D, Cabellos C, Dzupova O, Esposito S, Klein M, Kloek AT, et al. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect 2016;22:S37–62.

[20] Jolley KA, Bray JE, Maiden MC. Open-access bacterial population genomics: BIGSdb software, the PubMLST. org website and their applications. Wellcome Open Res 2018;3:3.

[21] Deghmane A-E, Hong E, Taha M-K. Emergence of meningococci with reduced susceptibility to third-generation cephalosporins. J Antimicrob Chemother 2016;72(1):95–8.

[22] Vigue L, Eyre-Walker A. The comparative population genetics of Neisseria meningitidis and Neisseria gonorrhoeae. PeerJ 2019;7:e7216.

[23] Igawa G, Yamagishi Y, Lee K-I, Dorin M, Shimuta K, Suematsu H, et al. Neisseria cinerea with high ceftriaxone MIC is a source of ceftriaxone and cefixime resistance-mediating penA sequences in Neisseria gonorrhoeae. Antimicrob Agents Chemother 2018;62(3). e02069-17.

[24] Ochiai S, Ishiko H, Yasuda M, Deguchi T. Rapid detection of the mosaic structure of the Neisseria gonorrhoeae penA gene, which is associated with decreased susceptibilities to oral cephalosporins. J Clin Microbiol 2008;46(5):1804–10.

[25] Chyou P-H. Patterns of bias due to differential misclassification by case–control status in a case–control study. Eur J Epidemiol 2007;22(1):7–17.

[26] Serra L, Presa J, Christensen H, Trotter C. Carriage of neisseria meningitidis in low and middle income countries of the Americas and Asia: a review of the literature. Infect Dis Ther 2020;9(2):209–40.

[27] Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci USA 2018;115(15):E3463–70. https://doi.org/10.1073/pnas.1717295115

[28] European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2015. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC. 2015.

[29] Kenyon C, Manoharan-Basil SS, Van Dijck C. Is there a resistance threshold for macrolide consumption? Positive evidence from an ecological analysis of resistance data from streptococcus pneumoniae, treponema pallidum, and mycoplasma genitalium. Microb Drug Resist 2021;27(8):1079–86.