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Global epidemiology of antimicrobial resistance in commensal *Neisseria* species: A systematic review

Thibaut Vanbaelen [a], Christophe Van Dijck [a,d], Jolein Laumen [a,d], Natalia Gonzalez [a], Irith De Baetselier [b], Sheeba S. Manoharan-Basil [a], Tessa De Block [a], Chris Kenyon [a,c,*]

[a] HIV/STI Unit, Institute of Tropical Medicine, Antwerp, Belgium
[b] Clinical Reference Laboratory, Institute of Tropical Medicine, Department of Clinical Sciences, Antwerp, Belgium
[c] Division of Infectious Diseases and HIV Medicine, University of Cape Town, Anzio Road, Observatory 7700, South Africa
[d] Laboratory of Medical Microbiology, University of Antwerp, Wilrijk, Belgium

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ABSTRACT

Background: Commensal *Neisseria* species (spp). represent an important reservoir of antimicrobial resistance genes for pathogenic *Neisseria* spp. In this systematic review, we aimed to assess the antimicrobial susceptibility of commensal *Neisseria* spp. and how this has evolved over time. We also aimed to assess if commensal *Neisseria* spp. showed intrinsic resistance to four antimicrobials - penicillin, azithromycin, ceftriaxone and ciprofloxacin.
Methods: Pubmed and Google Scholar were searched following the PRISMA guidelines. Articles reporting MICs of commensal *Neisseria* spp. were included according to inclusion/exclusion criteria, and the quality of the articles was assessed using a pre-designed tool. Individual and summary measures of penicillin, azithromycin, ceftriaxone and ciprofloxacin MICs were collected. Additional data was sought to perform a comparison between the MICs of pathogenic and commensal *Neisseria* spp.
Results: A total of 15 studies met our criteria.We found no evidence of intrinsic AMR in commensal *Neisseria* spp. We did find evidence of an increasing trend in MICs of commensal *Neisseria* spp. over time for all antimicrobials assessed. These findings were similar in various countries. Eight additional studies were included to compare pathogenic and commensal *Neisseria* spp.
Conclusion: The MICs of commensal *Neisseria* spp. appear to be increasing in multiple countries. Surveillance of MICs in commensals could be used as an early warning system for antimicrobial resistance emergence in pathogens. Our findings underline the need for antibiotic stewardship interventions, particularly in populations with high antimicrobial consumption.

1. Introduction

The genus *Neisseria* includes species that are both pathogenic (*Neisseria meningitidis* and *N. gonorrhoeae*) and commensals to humans (e.g., *N. cinerea, N. mucosa, N. subflava, N. lactamica*) (Dorey et al., 2019). The commensal *Neisseria* spp. are predominantly residents of the oropharynx and have been shown to play an important role in human health (Deasy et al., 2015; Liu et al., 2015). They come into frequent contact with pathogenic *Neisseria* spp. in the oropharynx, which provides the opportunity to exchange genetic material – predominantly via transformation (Spratt et al., 1992; Wadsworth et al., 2018; Fiore et al., 2020). Numerous studies have established that this genetic exchange is important in the genesis of resistance to antimicrobials in the pathogenic *Neisseria* spp. Wadsworth et al., (2018; Fiore et al., 2020). The most prominent genes involved in this transformation include *penA, mtrCDE, rplB, rplD, rplV* and *gyrA*. The acquisition of sections of these genes from commensal *Neisseria* spp. has played an important role in the acquisition of penicillin, cephalosporin, macrolide and fluoroquinolone resistance in *N. meningitidis/N. gonorrhoeae* (Wadsworth et al., 2018; Fiore et al., 2020; Manoharan-Basil et al., 2021).

Antimicrobial resistance (AMR) may emerge earlier and spread more extensively in commensals than in pathogenic *Neisseria* spp. (Fiore et al., 2020; Dong et al., 2020). This has led to call for surveillance of AMR in commensal *Neisseria* spp. (Fiore et al., 2020; Dong et al., 2019; Kenyon and Schwartz, 2018). Proponents of this view argue that commensals are more at risk for the emergence of AMR due to their considerably higher

* Corresponding author at: HIV/STI Unit, Institute of Tropical Medicine, Antwerp 2000, Belgium.
E-mail address: ckenyon@itg.be (C. Kenyon).

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prevalence (close to 100%) than that of pathogenic *Neisseria* spp. (typically 0.01–10%) (Dong et al., 2019; Kenyon and Schwartz, 2018). This higher prevalence means that commensals are more likely to be affected by bystander selection – selection for AMR by antimicrobials used for other indications (Tedijanto et al., 2018). It is not, however, known if relevant resistance associated mutations are more prevalent in commensal versus pathogenic *Neisseria* spp. In addition, it is unknown if commensal *Neisseria* spp. may be intrinsically resistant to certain classes of antimicrobials. If they are not, is the prevalence of AMR increasing in commensal *Neisseria* spp.?

To address these questions, we performed a systematic review of antimicrobial susceptibility in commensal *Neisseria* spp. Our overarching research question was how antimicrobial susceptibility in commensal *Neisseria* spp. has varied over place and time and in relation to the pathogenic *Neisseria* spp.

2. Methods

2.1. Systematic review of MICs in commensal Neisseria spp

This review was performed according to the PRISMA guidelines (Page et al., 2021). All the steps were performed independently by two reviewers (CK and TV). PRISMA checklists are presented in appendix A.

2.1.1. Search strategy

PubMed and Google Scholar were searched for articles published until March 21, 2021. Reference lists of relevant articles were checked for additional titles for inclusion in the review. Key words used for the search were “Antimicrobial Resistance”, “Antimicrobial Susceptibility”, “MIC”, “Minimum inhibitory concentration”,

“Neisseria” and specific names of each species of commensal *Neisseria* that has been isolated in humans (see appendix B).

2.1.2. Selection process and criteria

Titles and abstracts of all the articles retrieved through the search were screened. Duplicates were removed manually. Articles in German and Japanese were translated using DeepL Translator (www.deepl.com).

Articles reporting the MICs of commensal *Neisseria* spp. were included. Studies were included or excluded according to the following predefined criteria:

2.1.3. Inclusion criteria

1. Reports individual or summary measures of MICs of commensal *Neisseria* spp.
2. Abstracts and full text available
3. Drug sensitivity testing done in a laboratory setting
4. Clinic- and population-based samples, national surveillance samples and case series

2.1.4. Exclusion criteria

1. Case reports of single isolates
2. Studies that did not report the year or country the isolates were obtained from
3. Studies not reporting MICs of penicillin, ceftriaxone, ciprofloxacin or azithromycin.

2.1.5. Data extraction

Data extraction was done using a predesigned database using Microsoft Excel. Information extracted included article information (DOI, first author, year of publication, period of data collection and country), study design (population sampled, sample size), method of species ID and antimicrobial susceptibility testing methodology.

We extracted the following summary measures of MIC distribution in as far as they were reported: median, range, interquartile range (IQR), MIC 50, MIC 90 for each *Neisseria* species by study period and country. If those were not reported but individual measurements were, we calculated summary measures per species per study. Data was extracted for the following antimicrobials: penicillin, ceftriaxone, ciprofloxacin and azithromycin.

2.1.6. Article quality assessment

The quality and risk of bias of each article was assessed using a tool based on the review from Tadesse et al. Tadesse et al., (2017). This tool was modified for the purposes of this study and contained 11 criteria to evaluate study design, period and setting, sample collection, processing, storage and type of antimicrobial susceptibility testing performed (see appendix C). This quality assessment was not used for article inclusion/exclusion.

3. Comparison of MICs between *N. lactamica* and pathogenic Neisseria spp

In addition to the systematic analysis, we compared the MIC distributions of the pathogenic *Neisseria* spp. with those of *N. lactamica* per year and country. The rationale for this comparison was to assess if *N. lactamica* MICs (azithromycin, benzylpenicillin, ceftriaxone, ciprofloxacin) were different than those of *N. meningitidis* and *N. gonorrhoeae*. *N. lactamica* was chosen for these analyses as more data was available than for any other commensal. The main analysis was directed at the comparison between *N. lactamica* and *N. meningitidis* for three reasons: 1. There is sufficient data about those two species to perform a comparison; 2. These two species are frequently surveyed in the same programs; 3. Unlike *N. gonorrhoeae,* these species are not predominantly sexually transmitted and their prevalence and antimicrobial susceptibilities are less likely to be affected by differences in sexual behaviour and the intensity of Sexually Transmitted Infections control activities. Where studies reported relevant antimicrobial susceptibility data for both *N. lactamica* and *N. meningitidis*, this data was used. When this type of study was not available, a literature search was performed in PubMed and Google Scholar to find large well conducted surveys that assessed the corresponding MIC distributions in *N. meningitidis* and *N. gonorrhoeae*. Preference was given to studies reporting MIC distributions from the same city or country, same or similar year and that used a similar method to ascertain MIC. The only study providing antimicrobial susceptibility data for *N. lactamica* in Japan did so for cefotaxime, ampicillin, azithromycin and tosufloxacin (Takei et al., 2021). To enable comparisons, antibiotics from the same class were used as proxies for each other. Cefotaxime MICs was used as a proxy for ceftriaxone, ampicillin to represent penicillin and tosufloxacin to represent ciprofloxacin MICs. All MIC values were converted in mg/L.

3.1. Data analysis

We compared the changes in antimicrobial susceptibility per species over time in individual countries. We report all summary measures of antimicrobial susceptibility (median, IQR or range).

EUCAST (v. 11.0) breakpoints in *N. gonorrhoeae* were used to define AMR in all *Neisseria* species: ceftriaxone resistance, > 0.125 mg/L; ciprofloxacin resistance, > 0.06 mg/L; and benzylpenicillin resistance, > 1 mg/L (available at: http://www.eucast.org). The epidemiological cutoff of 1 mg/L was used for azithromycin as EUCAST does not provide a breakpoint for this antibiotic.

The results of the comparisons between commensal and pathogenic *Neisseria* spp. are presented graphically with forest plots for each antibiotic separately. Median MICs and range are displayed on the plots using a log2 scale.

Meta-analysis was not conducted because of the small number of isolates available per country per time point and variations in how antimicrobial susceptibility was determined and summarized. We did not conduct tests to assess if differences in MIC distributions were

statistically significant. This was related to factors such as differences in study design between samples being compared and the fact that none of the studies we reviewed provided individual sample level MIC data. Only a limited number of studies reported interquartile ranges and we thus used medians and ranges to compare MICs between groups. The graphics and calculations were produced using R version 4.0.2.

3.2. Intrinsic resistance

To evaluate if a *Neisseria* species exhibited evidence of intrinsic resistance to a particular antimicrobial, we assessed if any isolate of that species, including the older samples, had MICs below the EUCAST breakpoints for *N. gonorrhoeae*. If any isolates of a species were susceptible according to EUCAST breakpoints, then this species was classified as not having intrinsic resistance (Bengtsson-Palme and Larsson, 2016).

4. Results

A. Systematic review of MICs in commensal *Neisseria* spp.

The literature search identified 295 studies (Fig. 1). Of these 4 were excluded due to duplication, 274 were excluded based on title and abstract and 15 full-text articles were reviewed. Of these 8 studies met the inclusion/exclusion criteria. Seven studies were included through other sources which brings the total number of studies included in the review to 15 (Table 1).

4.1. Evolution of MICs in commensal Neisseria spp. over time

Table 2A contains all summary measures of MICs by study and species. The most relevant findings are highlighted hereunder.

4.2. N. cinerea

The earliest study to report antimicrobial susceptibilities was that of Berger et al., who found low penicillin MICs (range 0.00015–0.0006 mg/L in 28 clinical isolates of *N. cinerea* from Germany pre-1961 (Table 2A) (Berger and Paepcke, 1962). A different study reported a low penicillin MIC (0.04 mg/L) for one isolate of *N. cinerea* obtained from Germany in 1962 (Bowler et al., 1994). By the early 1980 s, penicillin MICs in this organism were higher than in the previous studies, between 0.125 and 1 mg/L in the USA (Knapp et al., 1984) and 0.16–0.64 mg/L in France (Bowler et al., 1994). A larger study conducted in France between 1973 and 1997 (n = 183) also showed high MICs (median MIC 0.5 mg/L; range 0.125–8) (Kochi et al., 1999).

4.3. N. subflava

A study from Belgium that used an identical protocol to compare the MICs of historical isolates from the early 1980 s with isolates obtained in 2019 found an increase in MICs over time (azithromycin: median 1–176 mg/L; ceftriaxone: median 0.03–0.38 mg/L (Laumen et al., 2021). The data from Asia shows that ceftriaxone MICs were higher in Vietnam in 2016 (median 0.064) than in Japan in 2005 (median 0.03) (Dong et al., 2019; Furuya et al., 2007). A small study from Spain in 1996 found high penicillin MICs in *N. subflava* (median 1 mg/L [range 0.06–4] and *N. mucosa* (median 1 mg/L [range 0.12–1] (Sáez Nieto et al., 1998).

4.4. Intrinsic resistance

We found no evidence of intrinsic antimicrobial resistance to any antimicrobial considered in any of the *Neisseria* species under review (Table 2A).

A. Comparison of MICs in pathogenic *Neisseria* spp. vs *N. lactamica*

To perform a comparison between pathogenic and commensal *Neisseria* spp., eight studies were included (6 of *N. gonorrhoeae* and 2 of *N. meningitidis* MICs). Relevant study characteristics are provided in Table 1. Studies from five countries included data that enabled us to compare MIC distributions between commensal *Neisseria* (*N. lactamica*) and *N. meningitidis*/*N. gonorrhoeae* (Fig. 2).

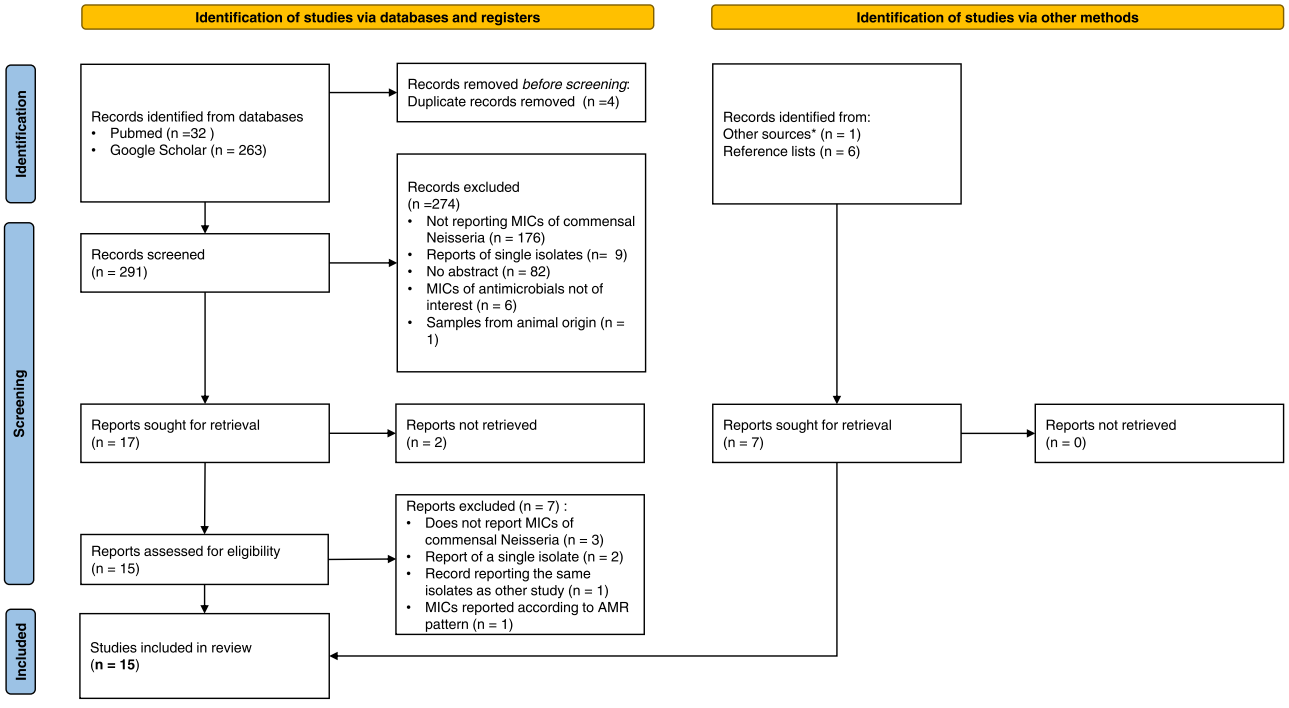

Fig. 1. Flowchart of study selection.

Table 1
Selected characteristics of the studies included in the systematic review and comparison of MICs between pathogenic Neisseria spp. and Neisseria lactamica.

Study First Author & reference	Year of publication	Study period	Country	Sampling method	Number of isolates	MIC testing methodology	Method of species ID	Species assessed	Relevant antimicrobials assessed
Studies included from the systematic review									
(Laumen et al., 2021)	2020	1979–1990	Belgium	29 isolates collected between 1979 and 1990 and kept in the Institute of Tropical Medical Medicine's historical collection of *Neisseria*.	29	Agar dilution	NS	Nm, Ns, No, Nma	Ceftriaxone, azithromycin
(Laumen et al., 2021)	2020	2019	Belgium	10 men with a diagnosis of anogenital Ng had their oropharynges swabbed on 2 separate occasions and all *Neisseria* cultured and MICs assessed	27	E-test	GS, O, MALDI-TOF	Nm, Ns, No, Nma, Ng	Ceftriaxone, azithromycin
(Laumen et al., 2022)	preprint	2019–2021	Belgium	A subgroup of 64 MSM using HIV pre-exposure prophylaxis of a randomized clinical trial (PreGo) and 20 employees of the Institute of Tropical Medicine.	26	E-test	GS, O, MALDI-TOF	Nm, Nl	Ceftriaxone, azithromycin, ciprofloxacin
(Chen et al., 2020)	2019	2005–18	China	198 N. meningitidis and 293 commensal *Neisseria* isolates collected between 2005 and 2018 in Shanghai. The *N. meningitidis* isolates were obtained from invasive meningococcal isolates (n = 46) and asymptomatic carriers (n = 152). The commensal *Neisseria* isolates were all obtained from carriers, including *N. lactamica* (n = 252).	491	Agar dilution	GS, O, MALDI-TOF	Nl, Np, Ns, Nc, Nmu, No, Nm	Ciprofloxacin
(Shen and Chen, 2020)	2019	2014–16	China	Carriage survey performed in 11 kindergartens and 15 schools in Shanghai. Posterior oropharyngeal swabs collected from 2239 children younger than 15 years.	200	Agar dilution	GS, O, MALDI-TOF	Nl	Ciprofloxacin
(Berger and Paepcke, 1962)	1962	1961	Germany	28 strains cultivated from the human pharynx. Further details pertaining to sample selection were not provided.	28	Agar dilution	GS, O, biochem	Nc	Penicillin
(Karch et al., 2015)	2015	1999–2000	Germany	*N. lactamica* strains (n = 123) collected during the Bavarian meningococcal carriage study in winter 1999/2000.	123	E-test	GS, O, biochem	Nl	Penicillin
(Karch et al., 2015)	2015	2006	Germany	*N. meningitidis* strains (n = 129) randomly selected from invasive isolates received by the German reference laboratory for meningococci in 2006.	129	E-test	GS, O, biochem	Nm	Penicillin
(Furuya et al., 2007)	2007	2005–2006	Japan	45 clinical isolates of *N. subflava* collected from the oropharynx of 40 Japanese men with urethritis and 5 women who were sex workers	45	Agar dilution	BD BBLCRYSTAL N/H, and VITEK NHI	Ns	Penicillin, ceftriaxone, ciprofloxacin
(Takei et al., 2021)	2020	2015	Japan	7 N. lactamica strains detected in Chiba Children's Hospital during the 2015 surveillance study for N. meningitidis were analyzed. Strains detected in specimens from 389 patients younger than 15 years who presented with respiratory symptoms.	7	Micro dilution	biochem, MALDI-TOF	Nl	Azithromycin, ampicillin, cefotaxime, tosufloxacin
(Sáez Nieto et al., 1998)	1998	NS	Spain	112 isolates cultured from oropharyngeal swabs from 40 randomly chosen individuals among university personnel	112	Agar dilution	GS, O, biochem	Nmu, Ns	Penicillin
(Arreaza et al., 2002)	2002	1996–8	Spain	286 isolates cultured during two meningococcal carriage surveys between 1996 and 1998	286	Agar dilution	GS, O, biochem	Nl	Penicillin, ciprofloxacin, ceftriaxone
	1999	1973–97	France		124	Agar dilution	GS, O, biochem	Nc	Penicillin

(*continued on next page*)

Table 1 (*continued*)

Study First Author & reference	Year of publication	Study period	Country	Sampling method	Number of isolates	MIC testing methodology	Method of species ID	Species assessed	Relevant antimicrobials assessed
(Kochi et al., 1999)				183 strains of *N cinerea*, isolated from various human biological specimens and sent to the National Meningococcal Reference Center between 1973 and 1997. MIC was defined for 124/183 strains.					
(Bowler et al., 1994)	1994	1962–82	France/ Germany	Four isolates of *N. cinerea*, 3 from France and one from Germany had their penicillin MICs assessed as part of a series of transformation experiments with Nm	4	NS	NS	Nc	Penicillin
(Knapp et al., 1984)	1984	1981–83	USA	Four isolates of *N. cinerea* were obtained from clinical isolates from various centres in the USA and further characterized	4	Agar dilution	GS, O, biochem	Nc	Penicillin
(Dong et al., 2019)	2021	2016–17	Vietnam	207 men who have sex with men had pharyngeal swabs performed and *Neisseria* species identified. We report results of patients who didn't report any antibiotic use in the past 6 months.	265	E-Test	GS, O, MALDI-TOF	Ng, Nm, Ns, Nmu, No	Ceftriaxone
(Saez Nieto et al., 1990)	1990	1979–1983	Spain	30 N. lactamica and 30 N. polysaccharea strains isolated from nasopharynges of children. Nm not included because strains described according to resistance pattern.	60	Agar dilution, disk diffusion	GS, O, biochem	Nl, Np	Penicillin, ceftriaxone
Studies included to perform a comparison between commensal and pathogenic Neisseria									
(Dong et al., 2020)	2020	2017	China	Neisseria gonorrhoeae isolates were collected from male patients with uncomplicated urogenital gonorrhea at the Shanghai Skin Disease Hospital in conjunction with the China GASP. The first 30 N. gonorrhoeae isolates of each month in 2017 (except for 36 isolates collected in July, making a total of 366 isolates)	366	Agar dilution	GS, O, biochem	Ng	Penicillin, ciprofloxacin, azithromycin, ceftriaxone
(Schafer et al., 1995)	1995	1988–1992	Germany	150 strains of Neisseria gonorrhoeae isolated between 1988 and 1992 from urethral, cervical, vaginal, anal and pharyngeal swabs in female prostitutes.	150	Agar dilution	GS, O, biochem	Ng	Penicillin, ciprofloxacin, azithromycin
(Arreaza et al., 2003)	2003	1997–98	Spain	2966 gonococcal isolates received at the Spanish National Reference Laboratory from 1983 to 2001. We used the results for the isolates from the years closest to those when the Nl isolates were obtained. (=1997–1998)	55	Agar dilution	NS	Ng	Penicillin, ceftriaxone, ciprofloxacin
(Arreaza et al., 2000)	2000	1996–97	Spain	789 isolates obtained from a study of asymptomatic Nm carriers (between 1996 and 1997). Results were reported separately for serogroup C (n = 89) and non-serogroup C (n = 700). We used the results for the larger sample size.	700	Agar dilution	GS, O, biochem	Nm	Penicillin, ceftriaxone, ciprofloxacin
(Watanabe et al., 2007)	2007	1990–2004	Japan	Strains isolated from meningococcal meningitis, pneumonia, and healthy carriers during a 15-year period from 1990 to 2004.	100	Agar dilution	NS	Nm	Penicillin, ceftriaxone, ciprofloxacin

(*continued on next page*)

Table 1 (*continued*)

Study First Author & reference	Year of publication	Study period	Country	Sampling method	Number of isolates	MIC testing methodology	Method of species ID	Species assessed	Relevant antimicrobials assessed
				100 strains of Nmen: 33 isolated from patients with meningococcal meningitis; 24 from patients with septicemia, pneumonia, rhinosinusitis, etc. other than meningitis.; 6 strains from STD, 33 strains from healthy carriers, 3 patient-derived strains, 1 unknown.					
(Hamasuna et al., 2013)	2013	2009–10	Japan	As part of a national surveillance project of Ng AMR, urethral swabs were obtained from male patients older than 16 years with symptoms of urethritis at 51 participating facilities including departments of urology in hospitals and private clinics that specialized in urology.	83	Agar dilution	NS and NAAT confirmed (Cobas amplicore STI-1)	Ng	Penicillin, ceftriaxone, ciprofloxacin, azithromycin
(Yang et al., 2006)	2006	2004–2005	China	Clinical N. gonorrhoeae isolates collected from 159 consecutive male patients with symptoms of urethritis at the Shanghai Skin Disease and STD Hospital between 2004 and 2005.	159	Agar dilution	GS, O, Biochem	Ng	Penicillin, ciprofloxacin, ceftriaxone
(De Baetselier, 2019)	NA	2019	Belgium	642 N. gonorrhoeae clinical isolates obtained during 2019 from participating centres were sent to the Belgian national Ng reference laboratory and had their MICs assessed	642	E-test, (Agar dilution)	NS	Ng	Ceftriaxone, azithromycin, ciprofloxacin

Abbreviation list: Biochem: biochemical tests, GS: gram staining, MALDI-TOF: Matrix-Assisted Laser Desorption/Ionization-Time Of Flight, MIC: minimum inhibitory concentration, NA: not applicable, NAAT: nuclei acid amplification tests, Nc: Neisseria cinerea, Ng: Neisseria gonorrhoeae, Nl: Neisseria lactamica, Nm: Neisseria meningitidis, Nma: Neisseria macacae, Nmu: Neisseria mucosa, No: Neisseria oralis, Np: Neisseria polysaccharea, Npe: Neisseria perflava, Ns: Neisseria subflava, Nsi: Neisseria sicca, NS: not specified, O: oxydase tests

4.4.1. Spain

Two large surveys of antimicrobial susceptibility in Spain in the 1990 s found higher penicillin MICs in *N. lactamica* (n = 286, median 0.25 mg/L [range 0.12–1]) than *N. meningitidis* (n = 700, median 0.06 mg/L [range 0.007–0.5]; Fig. 2; Table 2B) (Arreaza et al., 2002; Arreaza et al., 2000). A national survey in 1997–1998 found a gonococcal penicillin MIC distribution (median 0.25 mg/L [range <0.007–16]) which was similar to that of *N. lactamica* (Arreaza et al., 2003).

These same three surveys found similar ciprofloxacin MICs in the three species. The ciprofloxacin MICs were slightly higher in *N. lactamica* (median 0.003 mg/L [range 0.0015–0.5]), than *N. gonorrhoeae* (median 0.0015 mg/L [range <0.0015–0.25]) which was in turn slightly higher than those of *N. meningitidis* (median 0.006 mg/L [range 0.0003–0.012]).

The ceftriaxone MICs reported in these surveys were highest in *N. lactamica* (median 0.0015 mg/L [range 0.0007–0.06]), followed by *N. gonorrhoeae* (median 0.0007 mg/L [range 0.0003–0.007]) and then *N. meningitidis* (0.0007 mg/L [range 0.00007–0.015]).

A previous study of 30 *N. lactamica* strains from the early 80 s found lower MICs for both penicillin (median 0.2 mg/L; range 0.1–0.8) and ceftriaxone (median 0.0007 mg/L; range 0.003–0.0015) compared with the more recent studies (Saez Nieto et al., 1990).

4.4.2. Belgium

A study in Belgium evaluated the MICs of all oropharyngeal *Neisseria* spp. isolated from 96 individuals in 2019 (Laumen et al., 2022). MICs were found to be higher in *N. lactamica* than *N. meningitidis* for both azithromycin (median 1.5 mg/L [range 1–2] and 0.5 [range 0.19–6] mg/L, respectively) and ciprofloxacin (median 0.127 mg/L [range 0.06–0.19] and median 0.004 mg/L [range 0.002–0.125] but not ceftriaxone (median 0.008 mg/L [range 0.008–0.008] and median 0.008 mg/L [range 0.008–1]) (Fig. 2, Table 2B). Ceftriaxone (median 0.016 mg/L [range 0.016–0.5]) and ciprofloxacin (median 0.5 mg/L [range 0.002–32]) MICs were higher in 642 *N. gonorrhoeae* isolates evaluated in the Belgian national surveillance report for 2019 than the corresponding MICs for *N. lactamica* or *N. meningitidis* (De Baetselier, 2019). In contrast, the *N. gonorrhoeae* azithromycin MICs from this report (median 0.19 mg/L [range 0.03–256]) were lower than those for *N. lactamica* and *N. meningitidis*.

4.4.3. Germany

Karch et al., compared the penicillin MIC distributions of *N. lactamica* (n = 123, collected during a meningococcal carriage study in 1999/2000) and *N. meningitidis* (n = 129, randomly selected from invasive isolates received by the national reference laboratory in 2006) (Karch et al., 2015). The penicillin MICs were higher in *N. lactamica* (median 0.38; range 0.064–2 mg/L) than *N. meningitidis* (median 0.064; range 0.016–0.25 mg/L). These penicillin MICs in *N. lactamica* were also higher than those reported for 150 isolates of *N. gonorrhoeae* obtained between 1988 and 1992 (median 0.125 (range 0.002–128) (Schafer et al., 1995).

Table 2A
Summary measures of antimicrobial susceptibility by study and species – results of the systematic review.

Species	Year	Author	Country	Antimicrobial	N isolates	Median MIC (mg/L)	Range min (mg/L)	Range max (mg/L)
N. lactamica	1996–1998	(Arreaza et al., 2002)	Spain	penicillin	286	0,25	0,12	1
N. lactamica	1996–1998	(Arreaza et al., 2002)	Spain	ceftriaxone	286	0,0015	0,0007	0,06
N. lactamica	1996–1998	Arreaza (Arreaza et al., 2002)	Spain	ciprofloxacin	286	0003	0,0015	0,5
N. cinerea	1961	(Berger and Paepcke, 1962)	Germany	penicillin	28		0,00015	0,0006
N. cinerea	1962–1982	(Bowler et al., 1994)	France, Germany	penicillin	4	0,24	0,04	0,64
Various commensal *Neisseria* species	2005–2018	(Chen et al., 2020)	China	ciprofloxacin	293	0,25	0015	16
N. flavescens	2016–2017	(Dong et al., 2019)	Vietnam	ceftriaxone	76	0047	0047	
N. macacae	2016–2017	(Dong et al., 2019)	Vietnam	ceftriaxone	7	0047		
N. oralis	2016–2017	(Dong et al., 2019)	Vietnam	ceftriaxone	2	0056		
N. subflava	2016–2017	(Dong et al., 2019)	Vietnam	ceftriaxone	33	0064		
N. subflava	2005–2006	(Furuya et al., 2007)	Japan	penicillin G	45	0,5	0,06	2
N. subflava	2005–2006	(Furuya et al., 2007)	Japan	ceftriaxone	45	0,03	0001	0,12
N. subflava	2005–2006	(Furuya et al., 2007)	Japan	ciprofloxacin	45	0,25	0008	8
N. lactamica	1999–2000	(Karch et al., 2015)	Germany	penicillin G	123	0,38	0064	2
N. cinerea	1981–1983	(Knapp et al., 1984)	USA	penicillin	4		0125	1
N. cinerea	1973–1997	(Kochi et al., 1999)	France	penicillin	124	0,5	0125	8
N. lactamica	2019	(Laumen et al., 2022)	Belgium	azithromycin	2	1,5	1	2
N. lactamica	2019	(Laumen et al., 2022)	Belgium	ciproflocaxin	2	0127	0064	0,19
N. lactamica	2019	(Laumen et al., 2022)	Belgium	ceftriaxone	2	0008	0008	0008
N. subflava	2019	(Laumen et al., 2021)	Belgium	azithromycin	10	176	0047	256
N. subflava	2019	(Laumen et al., 2021)	Belgium	ceftriaxone	10	0,38	0023	2
N. macacae	2019	(Laumen et al., 2021)	Belgium	azithromycin	3	8	4	256
N. macacae	2019	(Laumen et al., 2021)	Belgium	ceftriaxone	3	0094	0032	0125
N. oralis	2019	(Laumen et al., 2021)	Belgium	azithromycin	2	3	3	3
N. oralis	2019	(Laumen et al., 2021)	Belgium	ceftriaxone	2	0273	0047	0,5
N. subflava	1983	(Laumen et al., 2021)	Belgium	azithromycin	7	1	0025	4
N. subflava	1983	(Laumen et al., 2021)	Belgium	ceftriaxone	7	0,03	0015	0,06
N. macacae	1983	(Laumen et al., 2021)	Belgium	azithromycin	5	8	4	8
N. macacae	1983	(Laumen et al., 2021)	Belgium	ceftriaxone	5	0,06	0,03	0125
N. oralis	1983	(Laumen et al., 2021)	Belgium	azithromycin	2	4	4	4
N. oralis	1983	(Laumen et al., 2021)	Belgium	ceftriaxone	2	0,06	0,06	0,06
Various commensal *Neisseria* species	1998	(Sáez Nieto et al., 1998)	Spain	penicillin			0,06	4
N. lactamica	1979–1983	(Saez Nieto et al., 1990)	Spain	ceftriaxone	30	0,0007	0,0003	0,0015
N. lactamica	1979–1983	(Saez Nieto et al., 1990)	Spain	penicillin	30	0,2	0,1	0,8
N. polysaccharea	1979–1983	(Saez Nieto et al., 1990)	Spain	ceftriaxone	30	0,0004	0,0003	0025
N. polysaccharea	1979–1983	(Saez Nieto et al., 1990)	Spain	penicillin	30	0,25	0,05	0,8
N. lactamica	2014, 2016	(Shen and Chen, 2020)	China	ciprofloxacin	200	0,25	0,06	1
N. lactamica	2015	(Takei et al., 2021)	Japan	azithromycin	7	1	0,25	1
N. lactamica	2015	(Takei et al., 2021)	Japan	ampicillin	7	1	0,5	4
N. lactamica	2015	(Takei et al., 2021)	Japan	tosufloxacine	7	0,5	0015	1
N. lactamica	2015	(Takei et al., 2021)	Japan	cefotaxime	7	1	1	8

4.4.4. China

A large clinical study from Shanghai between 2005 and 2018 found high ciprofloxacin MICs for *N. meningitidis* (median 0.125 mg/L; range 0.015–1) but even higher MICs in circulating commensal *Neisseria* spp. (median 0.25; range 0.015–16; Table 1; Fig. 2 (Chen et al., 2020)). A further survey conducted in Shanghai children between 2014 and 2016 found similarly high ciprofloxaxin MICs for *N. lactamica* (median 0.25; range 0.06–1) (Shen and Chen, 2020). Gonococcal ciprofloxacin MICs (n = 159) obtained in Shanghai in 2004–2005 were higher than both those for *N. meningitidis* and *N. lactamica* (median 8 mg/L [range 0.06–64] (Yang et al., 2006). A later study showed similarly high ciprofloxacin MICs for *N. gonorrhoeae* (n = 366) obtained in Shanghai in 2017 (median 16 mg/L [range 0.004–32]) (Dong et al., 2020).

4.4.5. Japan

Variations in the ciprofloxacin MICs between *Neisseria* species in Japan were very similar to those found in China with very high MICs in *N. gonorrhoeae* (median 8 mg/L; range 0.06–32), followed by *N. lactamica* (median 0.5 mg/L; range 0.015–1) and then *N. meningitidis* (median 0.004 mg/L; range 0.004–0.125; Table 1; Fig. 2) (Takei et al., 2021; Watanabe et al., 2007; Hamasuna et al., 2013). Penicillin MICs were also markedly elevated in *N. lactamica* (median 1 mg/L; range 0.5–4) and *N. gonorrhoeae* (median 1 mg/L; range 0.06–64) in comparison to *N. meningitidis* (median 0.031 mg/L; range 0.016–0.25) (Takei et al., 2021; Watanabe et al., 2007; Hamasuna et al., 2013). Ceftriaxone MICs were highest in *N. lactamica* (median 1 mg/L; range 1–8) followed by *N. gonorrhoeae* (median 0.06 mg/L; range 0.06–0.125) and *N. meningitidis* (median 0.004 mg/L; range 0.004–0.004) (Takei et al., 2021; Watanabe et al., 2007; Hamasuna et al., 2013).

5. Discussion

Although little has been published evaluating the antimicrobial susceptibility of commensal *Neisseria* spp., the data that has been published is instructive. Our findings suggest that commensal *Neisseria* spp. are not intrinsically resistant to the antimicrobials evaluated here when utilizing *N. gonorrhoeae* breakpoints. Thus *N. cinerea* was highly susceptible to penicillin in the 1960 s (Berger and Paepcke, 1962).

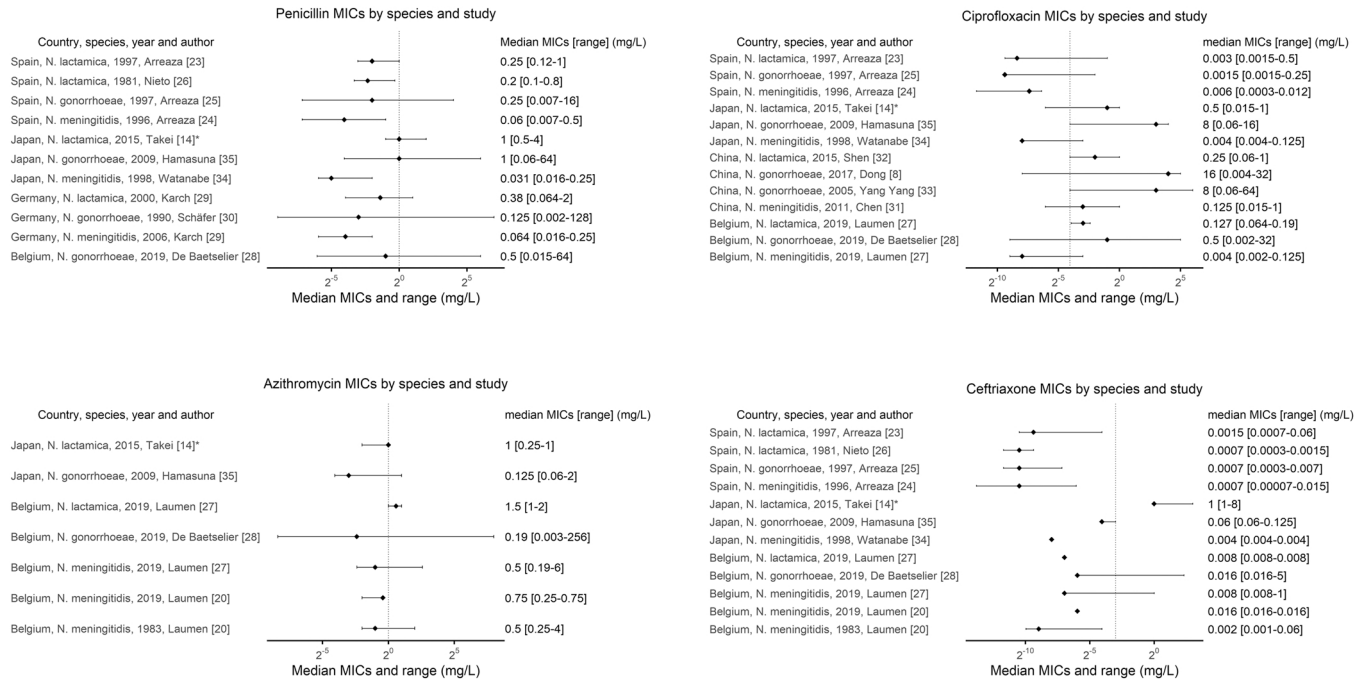

Fig. 2. Penicillin, Azithromycin, Ceftriaxone and Ciprofloxacin minimum inhibition concentrations (MICs, mg/L) median and range for *N. gonorrhoeae*, *N. meningitidis* and *N. lactamica* by study. The horizontal dotted line represents the EUCAST (v. 11.0) breakpoint or epidemiological cut-off for the corresponding antimicrobials. * For this study we used an antibiotic of the same class as proxies, cefotaxime for ceftriaxone, tosufloxacin for ciprofloxacin and ampicillin for penicillin.

Table 2B
Summary measures of antimicrobial susceptibility by study and species – results for pathogenic Neisseria species (studies included to perform a comparison between commensal and pathogenic Neisseria).

Species	Year	Author	Country	Antimicrobial	N isolates	Median MIC (mg/L)	Range min (mg/L)	Range max (mg/L)
N. gonorrhoeae	2019	(De Baetselier, 2019)	Belgium	azithromycin	642	0,19	0003	256
N. gonorrhoeae	2019	(De Baetselier, 2019)	Belgium	ceftriaxone	642	0016	0016	5
N. gonorrhoeae	2019	(De Baetselier, 2019)	Belgium	ciprofloxacin	642	0,5	0002	32
N. gonorrhoeae	2019	(De Baetselier, 2019)	Belgium	penicillin	642	0,5	0015	64
N. meningitidis	2019	(Laumen et al., 2022)	Belgium	azithromycin	34	0,5	0,19	6
N. meningitidis	2019	(Laumen et al., 2022)	Belgium	ciproflocaxin	34	0004	0002	0125
N. meningitidis	2019	(Laumen et al., 2022)	Belgium	ceftriaxone	34	0008	0008	1
N. meningitidis	2019	(Laumen et al., 2021)	Belgium	azithromycin	5	0,75	0,25	0,75
N. meningitidis	2019	(Laumen et al., 2021)	Belgium	ceftriaxone	5	0016	0016	0016
N. meningitidis	1983	(Laumen et al., 2021)	Belgium	azithromycin	15	0,5	0,25	4
N. meningitidis	1983	L(Laumen et al., 2021)	Belgium	ceftriaxone	15	0002	0001	0,06
N. gonorrhoeae	2004–2005	(Yang et al., 2006)	China	penicillin	159	32	0,05	64
N. gonorrhoeae	2004–2005	(Yang et al., 2006)	China	ciprofloxacin	159	8	0,06	64
N. gonorrhoeae	2004–2005	(Yang et al., 2006)	China	ceftriaxone	159	0,03	0004	0,25
N. gonorrhoeae	2017	(Dong et al., 2020)	China	ciprofloxacin	366	16	0004	32
N. meningitidis	2005–2018	(Chen et al., 2020)	China	ciprofloxacin	198	0125	0015	1
N. gonorrhoeae	1988–1992	(Schafer et al., 1995)	Germany	penicillin	150	0125	0002	128
N. meningitidis	2006	(Karch et al., 2015)	Germany	penicillin G	129	0064	0016	0,25
N. meningitidis	1990–2004	(Watanabe et al., 2007)	Japan	penicillin G	100	0031	0016	0,25
N. meningitidis	1990–2004	(Watanabe et al., 2007)	Japan	ceftriaxone	100	0004	0004	0004
N. meningitidis	1990–2004	(Watanabe et al., 2007)	Japan	ciprofloxacin	100	0004	0004	0125
N. gonorrhoeae	2009–2010	(Hamasuna et al., 2013)	Japan	penicillin G	83	1	0,06	64
N. gonorrhoeae	2009–2010	(Hamasuna et al., 2013)	Japan	ceftriaxone	83	0,06	0,06	0125
N. gonorrhoeae	2009–2010	(Hamasuna et al., 2013)	Japan	azithromycin	83	0125	0,06	2
N. gonorrhoeae	2009–2010	(Hamasuna et al., 2013)	Japan	ciprofloxacin	83	8	0,06	16
N. meningitidis	1996–1997	(Arreaza et al., 2000)	Spain	penicillin	700	0,06	0007	0,5
N. meningitidis	1996–1997	(Arreaza et al., 2000)	Spain	ceftriaxone	700	0,0007	0,00007	0015
N. meningitidis	1996–1997	(Arreaza et al., 2000)	Spain	ciprofloxacin	700	0006	0,0003	0012
N. gonorrhoeae	1997–1998	(Arreaza et al., 2003)	Spain	penicillin	55	0,25	0007	16
N. gonorrhoeae	1997–1998	(Arreaza et al., 2003)	Spain	ceftriaxone	55	0,0007	0,0003	0007
N. gonorrhoeae	1997–1998	(Arreaza et al., 2003)	Spain	ciprofloxacin	55	0,0015	0,0015	0,25
N. meningitidis	2016–2017	(Dong et al., 2019)	Vietnam	ceftriaxone	10	0002		

Penicillin MICs in this organism, however, appear to have increased steadily in the ensuing decades. A similar pattern has been established for *N. meningitidis* and *N. gonorrhoeae* (Kenyon et al., 2020; Wi et al., 2017). Of six bacterial species tested, *N. gonorrhoeae* was the most susceptible to penicillin in the early antibiotic era (Kenyon et al., 2020). Following decades of antibiotic exposure, penicillin MICs of

N. gonorrhoeae have increased considerably (Kenyon et al., 2020; Wi et al., 2017). By 2018, isolates with penicillin and ceftriaxone MICs of 1 mg/L or above were being reported from Japan (Igawa et al., 2018). Whilst there is considerably less data available for commensal *Neisseria* spp., the available data suggests that commensals have undergone a similar evolution. This is most evident for penicillin in *N. cinerea*, but likely also applies to *N. lactamica* and *N. subflava*. We found weak evidence that ceftriaxone, azithromycin, penicillin and ciprofloxacin MICs have been increasing in these species over the past few decades.

We also found specific populations where this increase seemed to be more pronounced. The median ciprofloxacin MICs for *N. lactamica, N. meningitidis* and *N. gonorrhoeae*, for example, were all higher in China than any other country included in our comparison. A systematic review of gonococcal antimicrobial resistance in China confirmed the high ciprofloxacin MICs but also documented how rapidly ciprofloxacin resistance emerged in China – ciprofloxacin resistance increased from 13% to 94% of gonococcal isolates between 1995 and 2003 (Chen et al., 2016).

A striking feature of our analysis was how much higher the ciprofloxacin MICs were in *N. lactamica* than *N. meningitidis* in China and elsewhere. In the studies we used from China, 98.5% of *N. lactamica* versus 68.7% of *N. meningitidis* were resistant to ciprofloxacin (Shen and Chen, 2020). Our comparison of MIC distributions revealed that, in general, the azithromycin, benzylpenicillin and ciprofloxacin MICs were higher in *N. lactamica* than *N. meningitidis.* As far as ceftriaxone was concerned, the same was true in one large study from Spain and one study from Japan, whereas in a smaller study from Belgium, the MIC distributions were very similar between these two species (Laumen et al., 2021; Arreaza et al., 2002; Arreaza et al., 2000). In general, MIC distributions for ceftriaxone in *N. gonorrhoeae* were higher than those of *N. meningitidis* and not too dissimilar to those of *N. lactamica*.

This high prevalence of resistance in commensal *Neisseria* spp. is more than a theoretical risk. Phylogenetic and transformation experiments have revealed that transformation from resistant isolates of *N. cinerea* was a likely source of penicillin and cephalosporin resistance in both *N. gonorrhoeae* and *N. meningitidis (*Igawa et al., 2018; Yahara et al., 2021). In the case of *N. gonorrhoeae,* epidemiological evidence pointed to Japan as one of the likely locations where this transformation occurred (Yahara et al., 2021). Phylogenetic analyses from China demonstrated that over half of the fluoroquinolone resistance conferring mutations in *N. meningitidis* were acquired from *N. lactamica (*Chen et al., 2020*)*. Similarly, increases in azithromycin resistance in *N. gonorrhoeae* have been linked to the spread of mosaic *mtrCDE* genes acquired from commensal *Neisseria* spp. Wadsworth et al., (2018). The incidence of this horizontal gene transfer (HGT) between *Neisseria* spp. is appreciable. One longitudinal study, for example, found evidence of HGT between *N. meningitidis* and *N. lactamica* in 15 loci over a 6 month period in the two individuals that were co-colonized by both bacteria at baseline (Pandey et al., 2018).

What is the reason for the increasing antimicrobial resistance in commensal *Neisseria* spp. ? Commensal *Neisseria* spp. are a key constituent of a healthy oro-pharyngeal microbiome (Aas et al., 2005; Willis and Gabaldon, 2020). Broad spectrum antimicrobials have been shown to be effective at eradicating the pathogenic *Neisseria* species, but to have little effect on the prevalence of commensal *Neisseria* species (de Block et al., 2021). Broad spectrum antimicrobials do however select for antimicrobial resistance in commensal *Neisseria* species (Laumen et al., 2022; de Block et al., 2021). Populations with high levels of antimicrobial consumption have been shown to be at high risk for the emergence of antimicrobial resistance in both *N. gonorrhoeae* (Kenyon and Schwartz, 2018; Kenyon et al., 2018; Kenyon et al., 2020; Lewis, 2013) and commensal *Neisseria* species (Laumen et al., 2022). Further research is required to beter define the types and intensity of antimicrobial exposure required to select for the genesis and spread of antimicrobial resistance of antimicrobial resistance in commensal *Neisseria (*Kenyon et al., 2021*)*.

There are a number of limitations to this review. Very few studies have been published on this topic. Those that have been published have numerous methodological weaknesses, including small sample sizes and non-random samples. Comparisons between studies are further hampered by differences in how species were identified and MICs assessed. For Japan we had to use antibiotics from the same class as proxies for the antibiotics of interest as no other data was available. Moreover, species identification in older studies might be subject to misclassification bias. Lastly, our definition of intrinsic resistance is based on EUCAST breakpoints for *N. gonorrhoeae* as no such breakpoints are defined for commensal *Neisseria* spp.

These limitations notwithstanding, our findings suggest the need to better understand and arrest the further emergence of AMR in commensal *Neisseria* spp. In the case of *N. gonorrhoeae*, a number of studies (but not all studies (Kirkcaldy et al., 2017)) have found a link between population level consumption of a class of antimicrobials and the prevalence of class concordant AMR (Kenyon et al., 2020; Kenyon et al., 2020). Various lines of evidence suggest that differential intensity of antimicrobial consumption is likely to be the key driver of AMR in commensal *Neisseria* spp. Dong et al., (2019; Laumen et al., 2021; Kenyon et al., 2021).

Taken as a whole, the findings of our review support the argument that surveillance of MICs of commensal *Neisseria* spp. may be a useful early warning system of excess antimicrobial exposure and increased risk for the emergence of AMR in *N. gonorrhoeae* and other pathogens (Kenyon et al., 2021). In a similar vein, the findings motivate for intensified antimicrobial stewardship. Whilst this is important in general populations, special attention should be focused on core-groups with high rates of partner change such as HIV pre-exposure prophylaxis cohorts due to the frequency with which gonococcal AMR has emerged in such populations (Kenyon and Schwartz, 2018; Lewis, 2013).

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Data Availability

The data we used is available from the publications listed in the methods section.

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Registration and protocol

This review was not registered. No protocol was prepared.

Transparency declarations

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.ijmm.2022.151551.

References

Aas, J.A., Paster, B.J., Stokes, L.N., Olsen, I., Dewhirst, F.E., 2005. Defining the normal bacterial flora of the oral cavity. J. Clin. Microbiol. 43 (11), 5721–5732. https://doi.org/10.1128/JCM.43.11.5721-5732.2005.

Arreaza, L., de La Fuente, L., Vázquez, J., 2000. Antibiotic susceptibility patterns ofneisseria meningitidis isolates from patients and asymptomatic carriers. Antimicrob. Agents Chemother. 44 (6), 1705–1707.
Arreaza, L., Salcedo, C., Alcala, B., Berron, S., Martin, E., Vazquez, J., 2003. Antibiotic resistance of Neisseria gonorrhoeae in Spain: trends over the last two decades. J. Antimicrob. Chemother. 51 (1), 153–156.
Arreaza, L., Salcedo, C., Alcala, B., Vazquez, J., 2002. What about antibiotic resistance in Neisseria lactamica? J. Antimicrob. Chemother. 49 (3), 545–547.
De Baetselier I. Belgian National Surveillance report for Neisseria gonorrhoeae, 2019,. 2020.
Bengtsson-Palme, J., Larsson, D.G., 2016. Concentrations of antibiotics predicted to select for resistant bacteria: proposed limits for environmental regulation. Epub 2015/11/23 Environ. Int. 86, 140–149. https://doi.org/10.1016/j.envint.2015.10.015.
Berger, U., Paepcke, E., 1962. Untersuchungen über die asaccharolytischen Neisserien des menschlichen Nasopharynx. Zeitschrift für Hygiene und Infektionskrankheiten, medizinische Mikrobiologie. Immunol. und Virol. 148 (4), 269–281.
de Block, T., Laumen, J.G.E., Van Dijck, C., Abdellati, S., De Baetselier, I., Manoharan-Basil, S.S., et al., 2021. WGS of commensal neisseria reveals acquisition of a new ribosomal protection protein (MsrD) as a possible explanation for high level azithromycin resistance in Belgium. Epub 2021/04/04 Pathogens 10 (3). https://doi.org/10.3390/pathogens10030384.
Bowler, L.D., Zhang, Q.-Y., Riou, J.-Y., Spratt, B.G., 1994. Interspecies recombination between the penA genes of Neisseria meningitidis and commensal Neisseria species during the emergence of penicillin resistance in N. meningitidis: natural events and laboratory simulation. J. Bacteriol. 176 (2), 333–337.
Chen, Y., Gong, Y., Yang, T., Song, X., Li, J., Gan, Y., et al., 2016. Antimicrobial resistance in Neisseria gonorrhoeae in China: a meta-analysis. Epub 2016/03/05 BMC Infect. Dis. 16, :108. https://doi.org/10.1186/s12879-016-1435-0.
Chen, M.L., Zhang, C., Zhang, X., Chen, M., 2020. Meningococcal quinolone resistance originated from several commensal neisseria species. Antimicrob. Agents Chemother. 64 (2). ARTN e01494-1910.1128/AAC.01494-19.
Deasy, A.M., Guccione, E., Dale, A.P., Andrews, N., Evans, C.M., Bennett, J.S., et al., 2015. Nasal inoculation of the commensal neisseria lactamica inhibits carriage of neisseria meningitidis by young adults: a controlled human infection study. Epub 2015/03/31 Clin. Infect. Dis. 60 (10), 1512–1520. https://doi.org/10.1093/cid/civ098.
Dong, H.V., Pham, L.Q., Nguyen, H.T., Nguyen, M.X.B., Nguyen, T.V., May, F., et al., 2019. Decreased Cephalosporin susceptibility of oropharyngeal neisseria species in antibiotic-using men-who-have-sex-with-men of Hanoi, Vietnam. Epub 2019/05/03 Clin. Infect. Dis.. https://doi.org/10.1093/cid/ciz365.
Dong, Y., Yang, Y., Wang, Y., Martin, I., Demczuk, W., Gu, W., 2020. Shanghai neisseria gonorrhoeae isolates exhibit resistance to extended-spectrum cephalosporins and clonal distribution. Epub 2020/10/31 Front. Microbiol. 11, 580399. https://doi.org/10.3389/fmicb.2020.580399.
Dorey, R.B., Theodosiou, A.A., Read, R.C., Jones, C.E., 2019. The nonpathogenic commensal Neisseria: friends and foes in infectious disease. Curr. Opin. Infect. Dis. 32 (5), 490–496.
Fiore, M.A., Raisman, J.C., Wong, N.R.H., Hudson, A.O., Wadsworth, C.B., 2020. Exploration of the neisseria resistome reveals resistance mechanisms in commensals that may be acquired by N. gonorrhoeae through horizontal gene transfer. Antibiotics-Basel 9 (10). ARTN 65610.3390/antibiotics9100656.
Furuya, R., Onoye, Y., Kanayama, A., Saika, T., Iyoda, T., Tatewaki, M., et al., 2007. Antimicrobial resistance in clinical isolates of Neisseria subflava from the oral cavities of a Japanese population. Epub 2007/11/06 J. Infect. Chemother. 13 (5), 302–304. https://doi.org/10.1007/s10156-007-0541-8.
Hamasuna, R., Yasuda, M., Ishikawa, K., Uehara, S., Takahashi, S., Hayami, H., et al., 2013. Nationwide surveillance of the antimicrobial susceptibility of Neisseria gonorrhoeae from male urethritis in Japan. J. Infect. Chemother. 19 (4), 571–578.
Igawa, G., Yamagishi, Y., Lee, K.I., Dorin, M., Shimuta, K., Suematsu, H., et al., 2018. Neisseria cinerea with High ceftriaxone MIC is a source of ceftriaxone and cefixime resistance-mediating pena sequences in neisseria gonorrhoeae. Epub 2018/01/10 Antimicrob. Agents Chemother. 62 (3). https://doi.org/10.1128/AAC.02069-17.
Karch, A., Vogel, U., Claus, H., 2015. Role of penA polymorphisms for penicillin susceptibility in Neisseria lactamica and Neisseria meningitidis. Epub 2015/09/01 Int. J. Med. Microbiol. 305 (7), 729–735. https://doi.org/10.1016/j.ijmm.2015.08.025.
Kenyon, C., Buyze, J., Spiteri, G., Cole, M., Unemo, M., 2020. Population-level antimicrobial consumption is associated with decreased antimicrobial susceptibility in Neisseria gonorrhoeae in 24 European countries: an ecological analysis. J. Infect. Dis. 221 (7), 1107–1116.
Kenyon, C., Buyze, J., Wi, T., 2018. Antimicrobial consumption and susceptibility of Neisseria gonorrhoeae: a global ecological analysis. Front. Med. 5, 329.
Kenyon, C., Laumen, J., Basil, S., 2021. Choosing new therapies for gonorrhoea: we need to consider the impact on the pan-neisseria genome. A Viewpoint. Antibiotics 10 (5), 515. https://doi.org/10.3390/antibiotics10050515.
Kenyon, Chris, Laumen, Jolein, Bossche, Dorien Van Den, Van Dijck, Christophe, 2020. Where ave all the susceptible gonococci gone? A historical review of changes in MIC distribution over the past 75 years. BMC Infect. Dis.
Kenyon, C., Laumen, J., Manoharan-Basil, S., 2021. Choosing new therapies for gonorrhoea: we need to consider the impact on the pan-neisseria genome. a viewpoint. Antibiotics 10 (5), 515.
Kenyon, C., Laumen, J., Van Dijck, C., De Baetselier, I., Abdelatti, S., Manoharan-Basil, S. S., et al., 2020. Gonorrhoea treatment combined with population-level general cephalosporin and quinolone consumption may select for Neisseria gonorrhoeae antimicrobial resistance at the levels of NG-MAST genogroup: an ecological study in Europe. J. Glob. Antimicro. Resist. 23, 377–384.
Kenyon, C., Laumen, J., Van Dijck, C., De Baetselier, I., Abdelatti, S., Manoharan-Basil, S. S., et al., 2020. Gonorrhoea treatment combined with population-level general cephalosporin and quinolone consumption may select for Neisseria gonorrhoeae antimicrobial resistance at the levels of NG-MAST genogroup: an ecological study in Europe. Epub 2020/11/19 J. Glob. Antimicrob. Resist.. https://doi.org/10.1016/j.jgar.2020.10.022.
Kenyon, C.R., Schwartz, I.S., 2018. Effects of sexual network connectivity and antimicrobial drug use on antimicrobial resistance in neisseria gonorrhoeae. Epub 2018/06/19 Emerg. Infect. Dis. 24 (7), 1195–1203. https://doi.org/10.3201/eid2407.172104.
Kirkcaldy, R.D., Bartoces, M.G., Soge, O.O., Riedel, S., Kubin, G., Del Rio, C., et al., 2017. Antimicrobial drug prescription and neisseria gonorrhoeae susceptibility, United States, 2005-2013. Epub 2017/09/21 Emerg. Infect. Dis. 23 (10), 1657–1663. https://doi.org/10.3201/eid2310.170488.
Knapp, J.S., Totten, P.A., Mulks, M.H., Minshew, B.H., 1984. Characterization of Neisseria cinerea, a nonpathogenic species isolated on Martin-Lewis medium selective for pathogenic Neisseria spp. Epub 1984/01/01 J. Clin. Microbiol. 19 (1), 63–67. https://doi.org/10.1128/JCM.19.1.63-67.1984.
Kochi, C.V., Guibourdenche, M., Lemeland, J.F., Riou, J.Y., 1999. Neisseria cinerea, a bacterium whose bacteriological identification is difficult. Epub 2002/02/20 Clin. Microbiol. Infect. 5 (10), 647–650. https://doi.org/10.1111/j.1469-0691.1999.tb00424.x.
Laumen, J.G.E., Van Dijck, C., Abdellati, S., De Baetselier, I., Manoharan-Basil, S.S., Van den Bossche, D., et al., 2022. Antimicrobial susceptibility of commensal Neisseria in a general population and men who have sex with men in Belgium. Sci. Rep. 12 (9).
Laumen, J.G.E., Van Dijck, C., Abdellati, S., Manoharan-Basil, S.S., De Baetselier, I., Martiny, D., et al., 2021. Markedly reduced azithromycin and ceftriaxone susceptibility in commensal neisseria species in clinical samples from Belgian men who have sex with men. Epub 2021/01/28 Clin. Infect. Dis. 72 (2), 363–364. https://doi.org/10.1093/cid/ciaa565.
Lewis, D.A., 2013. The role of core groups in the emergence and dissemination of antimicrobial-resistant N gonorrhoeae. Sex. Transm. Infect. 89 (4), 47–51. https://doi.org/10.1136/sextrans-2013-051020.
Lewis, D.A., 2013. The role of core groups in the emergence and dissemination of antimicrobial-resistant N gonorrhoeae. Sex. Transm. Infect. 89 (4), iv47–iv51. https://doi.org/10.1136/sextrans-2013-051020. PubMed PMID: 24243880.
Liu, G., Tang, C.M., Exley, R.M., 2015. Non-pathogenic Neisseria: members of an abundant, multi-habitat, diverse genus. Epub 2015/03/31 Microbiology 161 (7), 1297–1312. https://doi.org/10.1099/mic.0.000086.
Manoharan-Basil, S.S., Laumen, J.G.E., Van Dijck, C., Block, Td, Baetselier, I.D., Kenyon, C., 2021. Evidence of horizontal gene transfer of 50S ribosomal genes rplB, rplD, and rplY in Neisseria gonorrhoeae. Front. Microbiol. 12, 1263.
Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., et al., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Epub 2021/04/02 J. Clin. Epidemiol. 134, 178–189. https://doi.org/10.1016/j.jclinepi.2021.03.001.
Pandey, A., Cleary, D.W., Laver, J.R., Gorringe, A., Deasy, A.M., Dale, A.P., et al., 2018. Microevolution of Neisseria lactamica during nasopharyngeal colonisation induced by controlled human infection. Epub 2018/11/14 Nat. Commun. 9 (1), 4753. https://doi.org/10.1038/s41467-018-07235-5.
Saez Nieto, J.A., Lujan, R., Martinezsuarez, J.V., Berron, S., Vazquez, J.A., Vinas, M., et al., 1990. Neisseria-lactamica and neisseria-polysaccharea as possible sources of meningococcal beta-lactam resistance by genetic-transformation. Antimicrob. Agents Chemother. 34 (11), 2269–2272. https://doi.org/10.1128/Aac.34.11.2269.
Sáez Nieto, J.A., Marcos, C., Vindel, A., 1998. Multicolonization of human nasopharynx due to Neisseria spp. Int. Microbiol. 1 (1), 59–63.
Schafer, V., Enzensberger, R., Schneider, C., Rickmann, J., Nitschke-Ozbay, H., Brade, V., 1995. Epidemiology of penicillin-resistant Neisseria gonorrhoeae in Frankfurt, Germany. Epub 1995/10/01 Eur. J. Clin. Microbiol. Infect. Dis. 14 (10), 914–918. https://doi.org/10.1007/BF01691501.
Shen, Y.F., Chen, M.L., 2020. Prevalence, sequence type, and quinolone resistance of Neisseria lactamica carried in children younger than 15 years in Shanghai, China. J. Infect. 80 (1), 61–68. https://doi.org/10.1016/j.jinf.2019.08.020.
Spratt, B.G., Bowler, L.D., Zhang, Q.Y., Zhou, J., Smith, J.M., 1992. Role of interspecies transfer of chromosomal genes in the evolution of penicillin resistance in pathogenic and commensal Neisseria species. Epub 1992/02/01 J. Mol. Evol. 34 (2), 115–125. https://doi.org/10.1007/BF00182388.
Tadesse, B.T., Ashley, E.A., Ongarello, S., Havumaki, J., Wijegoonewardena, M., Gonzalez, I.J., et al., 2017. Antimicrobial resistance in Africa: a systematic review. Epub 2017/09/13 BMC Infect. Dis. 17 (1), 616. https://doi.org/10.1186/s12879-017-2713-1.
Takei, H., Takeuchi, N., Hoshino, T., Ohkusu, M., Segawa, S., Murata, S., et al., 2021. Bacteriological analysis of Neisseria lactamica isolated from the respiratory tract in Japanese children. Epub 2020/09/03 J. Infect. Chemother. 27 (1), 65–69. https://doi.org/10.1016/j.jiac.2020.08.011.
Tedijanto, C., Olesen, S.W., Grad, Y.H., Lipsitch, M., 2018. Estimating the proportion of bystander selection for antibiotic resistance among potentially pathogenic bacterial flora. Epub 2018/12/19 Proc. Natl. Acad. Sci. U.S.A. 115 (51), E11988–E11995. https://doi.org/10.1073/pnas.1810840115.
Wadsworth, C.B., Arnold, B.J., Sater, M.R.A., Grad, Y.H., 2018. Azithromycin resistance through interspecific acquisition of an epistasis-dependent efflux pump component and transcriptional regulator in Neisseria gonorrhoeae. Mbio. 9 (4). ARTN e01419-1810.1128/mBio.01419-18.

Watanabe, Y., Takahashi, C., Ohya, H., Okazaki, N., Onoue, Y., 2007. Antibiotic susceptibility of Neisseria meningitidis from healthy and diseased persons in Japan. Kansenshogaku zasshi J. Jpn. Assoc. Infect. Dis. 81 (6), 669–674.

Willis, J.R., Gabaldon, T., 2020. The human oral microbiome in health and disease: from sequences to ecosystems. Epub 2020/02/28 Microorganisms 8 (2). https://doi.org/10.3390/microorganisms8020308.

Wi, T., Lahra, M.M., Ndowa, F., Bala, M., Dillon, J.R., Ramon-Pardo, P., et al., 2017. Antimicrobial resistance in Neisseria gonorrhoeae: Global surveillance and a call for international collaborative action. Epub 2017/07/08 PLoS Med. 14 (7), e1002344. https://doi.org/10.1371/journal.pmed.1002344.

Yahara, K., Ma, K.C., Mortimer, T.D., Shimuta, K., Nakayama, S.-i, Hirabayashi, A., et al., 2021. Emergence and evolution of antimicrobial resistance genes and mutations in Neisseria gonorrhoeae. Genome Med. 13 (1), 1–12.

Yang, Y., Liao, M.M., Gu, W.M., Bell, K., Wu, L., Eng, N.F., et al., 2006. Antimicrobial susceptibility and molecular determinants of quinolone resistance in Neisseria gonorrhoeae isolates from Shanghai. J. Antimicrob. Chemother. 58 (4), 868–872. https://doi.org/10.1093/jac/dkl301.