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EPIDEMIOLOGICAL TRENDS OF ANTIBIOTIC-RESISTANT *NEISSERIA GONORRHEA* IN THE EU/EEA/EUROPEAN REGION: A SYSTEMATIC REVIEW

TRENDY EPIDEMIOLOGICZNE DOTYCZĄCE ANTYBIOTYKOOPORNEJ *NEISSERIA GONORRHEA* W REGIONIE UE/EOG/EUROPY: PRZEGLĄD SYSTEMATYCZNY

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Wkład autorów:
A. Study design/planning
zaplanowanie badań
B. Data collection/entry
zebranie danych
C. Data analysis/statistics
dane – analiza i statystyki
D. Data interpretation
interpretacja danych
E. Preparation of manuscript
przygotowanie artykułu
F. Literature analysis/search
wyszukiwanie i analiza literatury
G. Funds collection
zebranie funduszy

Summary

Neisseria gonorrhea is becoming more resistant to available antibiotic treatments. The growing antibiotic resistance of *Neisseria gonorrhea* in clinical isolates has been observed by different national surveillance systems around the globe and is posing a serious public health risk. The EU/EEA/European region is equally impacted by this developed antibiotic resistance in *Neisseria gonorrhea* isolates. Hence, this systematic review is focused to uncover the antibiotic resistance patterns of *Neisseria gonorrhea* across different countries in the EU/EEA/European region. The database PubMed and journal "Eurosurveillance" were used to search for the articles published between 2000-2020. Eight analytical studies that filled the selection criteria were included in the review. In the EU/EEA/European region, susceptibility and resistance of *Neisseria gonorrhea* toward different antibiotics varied from country to country. *Neisseria gonorrhea* displayed higher susceptibility toward spectinomycin and azithromycin and also displayed a high level of resistance to ciproflaxin and penicillin. With the antibiotics that are currently effective, there is a higher chance that *Neisseria gonorrhea* will develop gradual resistance toward those antibiotics in future too. Therefore, continuous surveillance of antibiotic-resistant *Neisseria gonorrhea* and health promotion awareness programs, and also investments in new effective antibiotic inventions can be helpful to tackle this issue.

Keywords: *Neisseria gonorrhea*, drug resistance, bacterial infections, sexually transmitted diseases, epidemiology

Streszczenie

Neisseria gonorrhea staje się w coraz większym stopniu oporna na dostępne antybiotyki. Rosnącą oporność *Neisseria gonorrhea* na antybiotyki w izolatach klinicznych zaobserwowano za pośrednictwem różnych krajowych systemów nadzoru na całym świecie i stanowi ona poważne zagrożenie dla zdrowia publicznego. Region UE/EOG/ Europy jest w równym stopniu dotknięty rozwiniętą opornością na antybiotyki u izolatów *Neisseria gonorrhea*. Z tego względu niniejszy systematyczny przegląd koncentruje się na opisie wzorców oporności *Neisseria gonorrhea* na antybiotyki w różnych krajach UE/EOG/ Europy. Do wyszukania artykułów opublikowanych w latach 2000-2020 wykorzystano bazę danych PubMed oraz czasopismo „Eurosurveillance". Do przeglądu włączono osiem badań analitycznych, które spełniły kryteria wyboru. W regionie UE/EOG/Europy wrażliwość i oporność *Neisseria gonorrhea* na różne antybiotyki różniła się w zależności od kraju. *Neisseria gonorrhea* wykazywała większą wrażliwość na spektynomycynę i azytromycynę, a także wykazywała wysoki poziom oporności na cyproflaksynę i penicylinę. Przy uwzględnieniu obecnie skutecznych antybiotyków istnieje większe prawdopodobieństwo, że *Neisseria gonorrhea* rozwinie stopniową oporność również na te antybiotyki w przyszłości. Dlatego też ciągłe monitorowanie opornych na antybiotyki bakterii *Neisseria gonorrhea* i zapewnienie programów uświadamiających w zakresie promocji zdrowia, a także inwestycji w nowe skuteczne rozwiązania z zakresu antybiotyków mogą być pomocne w rozwiązaniu tego problemu.

Słowa kluczowe: *Neisseria gonorrhea*, lekooporność, infekcje bakteryjne, choroby przenoszone drogą płciową, epidemiologia

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Introduction

Gonorrhea is an infectious disease caused by a bacteria called *Neisseria gonorrhea* and it is easily transmissible through unprotected sexual acts. The infection may lead from mild to serious health complications such as pelvic inflammatory disease, infertility, septic arthritis, peritonitis, chronic pain, and chronic inflammation in different parts of the body [1]. Currently, the most effective treatment against gonorrhea is antibiotic therapy. However, the growing susceptibility and resistance against antibiotics among *Neisseria gonorrhea* strains threaten the effectiveness of currently available antibiotics. Pathogenic resistance is more common against first-line antibiotics, whereas third-generation antibiotics are still considered effective against *Neisseria gonorrhea*. Nevertheless, there is growing uncertainty regarding the effectiveness of third-generation antibiotics due to several treatment failures reported in different nations, including Canada [2], South Africa [3], Australia [4], Japan [5], and the European Union [6-7]. For this reason and to keep antibiotic therapy effective, different health agencies around the world suggest using a combination of antibiotics to treat gonorrhea effectively [8].

"The Gonorrhea – Annual Epidemiological Report" published by the European Center of Disease Prevention and Control reported around 100673 gonorrhea cases in 2018 (with an overall rate of 26.4 cases per 100000 population) in the EU/EEA/European region countries. While the infection rates varied from country to country in the EU/EEA/European region, the highest incidence and prevalence rate was recorded in the Northern European countries. Additionally, men who have sex with men accounted for nearly half of the reported cases (48%) in 2018. Overall, there has been a nearly 22% increase in the overall notification rate of infection in 2018 compared to a 17% increase in 2017 [9,10]. This gradual increase in notification rate is alarming and serves as a breeding ground for antibiotic-resistant *Neisseria gonorrhea* strains.

Aim of the work

The aim of this review is to utilize the data from different analytical studies conducted in the EU/EEA and European region countries to understand antibiotic susceptibility and resistance among *Neisseria gonorrhea* in aforementioned area. This understanding will be a stepping stone to emphasize the development of new approaches for the management of gonorrhea infection and highlight the importance of public awareness regarding antibiotic abuse to protect public health.

Methodology

Protocol

This systematic review is conducted according to the PRISMA guidelines (Figure 1).

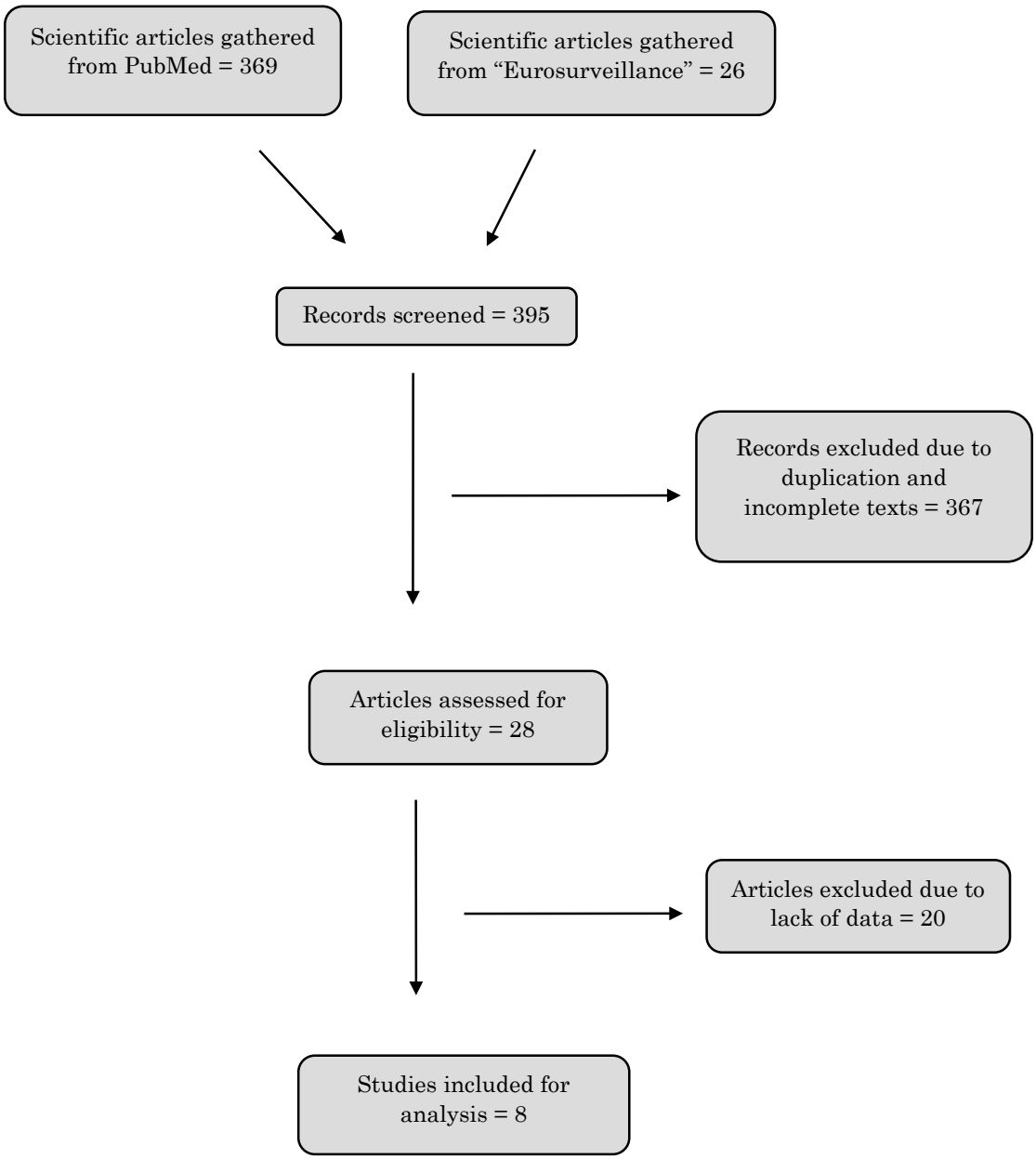

Figure 1. Flow diagram – study selection

Search Strategy

The scientific database "PubMed" was utilized to search the relevant articles published between the years 2000 and 2020. To search for the studies reporting on the trends of resistance toward antibiotics among *Neisseria gonorrhea*, data was retrieved from PubMed by using the following terms and combinations of terms: ''gonorrhea'' OR "*gonorrhea Neisseria*" AND "antibiotic resistance" OR ''antimicrobial resistance'' AND "Europe" OR "the EU" OR ''the EEA'' AND "analytical studies" OR "surveillances" OR '' national surveillances'' OR ''observational studies". In addition to PubMed, the journal named ''Eurosurveillance'' was also used as an additional source to search for appropriate articles. This journal was utilized because ''Eurosurveillance'' routinely publishes reports and articles on the prevalence and distribution of infectious diseases around the European Union and the European Economic Area. Thus, for purposes of systematic review it was considered a useful resource to find the target studies in the target regions.

Inclusion Criteria

- Studies must be in the English language.
- Studies must be either analytical or observational or a national surveillance.
- Studies focused on the antibiotic resistance of *gonorrhea Neisseria*.
- Studies were conducted in the EU/EEA/European region.
- Isolated *Neisseria gonorrhea* strains were from human clinical samples.

Data Retrieval

The articles were scrutinized to identify the data on author name, publication date, location, subject numbers, subjects age frequency, source of isolation, the total number of isolates, surveillance and intervention period, type of antibiotics, minimum inhibitory concentration range (MIC range), and susceptibility (S), intermediate susceptibility (I), and resistance (R) in percentage according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints. EUCAST is a global susceptibility examining committee. It is regulated by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID). It performs its role as the breakpoint advisory board of the European Medicines Agency (EMA) [11].

Quality Assessment

The quality of the studies was assessed on several factors, including selection bias, detection bias, attribution bias and reporting bias. The studies were assessed with seven points scoring. The points were attributed to the studies according to the requirements of quality assessment. Table 1 shows the complete list of factors and scoring.

Table 1. Quality assessment criteria and bias reporting scores for the scientific articles

Quality assessment criteria		
Category	**Sub-category**	**Score points**
Selection bias	Methods of the study	0 = Unclear 1 = Partially Clear 2 = Fully Clear
Detection bias	Outcome assessment	0 = Unclear 1 = Partially Clear 2 = Fully Clear
Attribution bias	Outcome data	0 = Unclear 1 = Partially Clear 2 = Fully Clear
Reporting bias	Selective reporting	0 = Outcome measure reported without explanation 1 = Outcome measure reported with explanation

Results

Figure 1 demonstrates the review process step by step. In total, 369 articles were found in PubMed, and 26 articles were retrieved from the journal ''Eurosurveillance.'' Thus, a total of 395 articles were chosen for consideration. Of these, 367 articles were excluded due to duplication and incomplete texts. The remaining 28 articles were retained based on the information drawn from the titles and abstracts. After reading the full text of each of the 28 articles, a further 20 articles were excluded for not fulfilling the selection criteria (missing data). Ultimately, eight studies fulfilling the inclusion criteria were included in the systematic review.

Characteristics of studies

The main characteristics of the studies are presented in Table 2. Of the eight studies, one was conducted in Spain [12], one in Germany [13], one in Greece [14], one in Greenland [15], one in Switzerland [16], and three in the Netherlands [17-19]. Gender distribution varied from study to study. Surveillance from Spain [12] and Switzerland [16] classified the subjects as males, females, and unknown. Whereas studies from Greenland [15] and Germany [13] reported subjects only as males and females, and two studies from the Netherlands [18,19] categorized the subjects as males, females, and homosexual males, while one study from the Netherlands [17] focused only on homosexual men. Furthermore, one study from Greece [14] did not mention any information on gender distribution.

Table 2. Summary of the main characteristics of included studies and their respective quality assessment scores

Study	Location	Source of isolates	Subjects	Age	Source of cultured samples	Total number of isolates	Observational period	Quality score
Regnath et al. 2016 [13]	Germany	Private medical practitioners	Male = 107 Female = 327	16-76	Urine, swabs	434	2004-2015	7
Tzelepi et al. 2010 [14]	Greece	Andreas Sygros STD hospital, Hospital of Venereal Diseases, other national hospitals	NA	NA	NA	635	2005-2008	4
Pederson et al. 2016 [15]	Greenland	Queen Ingrid Primary Health Care Centre	Male = 81 Female = 21	22-41	Urethra, cervix	102	2012-2015	7
Kovari et al. 2013 [16]	Switzerland	Regions of Zurich and north-eastern Switzerland	Males = 168 Female = 35 Unknown = 9	16-86	Urethra, cervix, anorectum, pharynx, joint and eye, involves unknown sites	210	2005-2012	6
Salmeron et al. 2020 [12]	Spain	Drassanes STI unit, primary healthcare units, other HUVH departments	Male = 1888 Female = 89 Unknown = 2	20-50	Urethral, rectal, vaginal, endocervical, pharynx	2036	2013-2017	7
Hofstraat et al. 2018 [19]	The Netherlands	19 of a total 25 STI centers in the Netherlands	Male = 2526 Female = 1754 Homosexual men = 7488	25-35	Pharyngeal, rectal, urethral, pharyngeal, cervical, swab	11768	2007-2015	7

Study	Location	Source of isolates	Subjects	Age	Source of cultured samples	Total number of isolates	Observational period	Quality score
De Vries et al. 2009 [17]	The Netherlands	The Amsterdam STI outpatient clinic	Homosexual men = 1075	NA	Urethra, rectum, pharynx	1231	2006-2008	7
Wind et al. 2016 [18]	The Netherlands	The Amsterdam STI outpatient clinic	Male = 436 Female = 397 Homosexual men = 2318	20-43	Urethra, rectum, cervix, pharynx	3151	2012-2015	7

The collective age of subjects ranged from 16-86 years in all the studies. However, in two studies [14,17] the data on age was missing. Additionally, in all the studies, the isolated samples were extracted from different body parts such as the urethra, cervix, vagina, rectum, pharynx, eyes, and some unknown sites. Nevertheless, this data regarding the isolated samples was missing in the study from Greece [14]. The source of the cultured samples in all the studies were public hospitals, private clinics and other national STI (sexually transmitted infection) units.

Antibiotic susceptibility and resistance

The susceptibility, resistance, MIC (Minimum Inhibitory Range) with respective locations and the antibiotics are presented in Table 3.

Table 3. EUCAST Percentage of susceptibility, intermediate susceptibility, resistance, MIC (Minimum Inhibitory Range) with respective locations and antibiotics

Antibiotic	Class of antibiotics	Study	Location	MIC range	EUCAST		
					Susceptible (%)	Intermediate (%)	Resistant (%)
Azithromycin	Macrolide	Regnath et al. 2016 [13]	Germany	0.016-128 mg/L	73.5	21.0	5.5
		Wind et al. 2016 [18]	the Netherlands	0.016-256 mg/L	90.1	8.7	1.3
		Pederson et al. 2016 [15]	Greenland	0.023-0.125 mg/L	100	0	0
		Hofstraat et al. 2018 [19]	the Netherlands	0.0-1.0 mg/L	NA	Men = 0.8 Women = 0.9 Homosexual men = 2.0	Men = 2.5 Women = 2.9 Homosexual men = 5.7
		Salmeron et al. 2020 [12]	Spain	0.016-256 mg/L	97.4	0	2.6
Cefixime	Cephalosporin	Regnath et al. 2016 [13]	Germany	0.016-0.125 mg/L	100	0	0
		Kovari et al. 2013 [16]	Switzerland	>0.125 mg/L	NA	11.1	NA
		Salmeron et al. 2020 [12]	Spain	0.016-0.38 mg/L	95.1	0	4.9

Antibiotic	Class of antibiotics	Study	Location	MIC range	EUCAST		
					Susceptible (%)	Intermediate (%)	Resistant (%)
Ceftriaxone	**Cephalosporin**	Regnath et al. 2016 [13]	Germany	0.002-0.125 mg/L	100	0	0
		Pederson et al. 2016 [15]	Greenland	0.002-0.006 mg/L	100	0	0
		Wind et al. 2016 [18]	the Netherlands	0.002-0.125 mg/L	92	8	0
		Kovari et al. 2013 [16]	Switzerland	>0.125 mg/L	NA	3.5	NA
		Hofstraat et al. 2018 [19]	the Netherlands	>0.032 mg/L	NA	Men =1.2 Women =2.4 Homosexual men = 3.9	Men = 0 Women = 0 Homosexual men = 0
		Salmeron et al. 2020 [12]	Spain	0.016-0.38 mg/L	99.7	0	0.3
Ciprofloxacin	**Fluoroquinolones**	De Vries et al. 2009 [17]	the Netherlands	>1.0 ug/ml	NA	NA	44.4
		Tzelepi et al. 2010 [14]	Greece	0.002-32 ug/ml	51.7	0.3	48.0
		Regnath et al. 2016 [13]	Germany	0.002-32 mg/L	29.5	0.2	70.3
		Kovari et al. 2013 [16]	Switzerland	>0.064 mg/L	NA	NA	69.0
		Salmeron et al. 2020 [12]	Spain	0.002-32 mg/L	48.6	0.2	51.3
Cefotaxime	**Cephalosporin**	Tzelepi et al. 2010 [14]	Greece	0.25-1 mg/L	7.5	NA	0.3
		Hofstraat et al. 2018 [19]	the Netherlands	>0.125 mg/L	NA	NA	Men = 2.8 Women = 3.0 Homosexual men = 5.5
Chloramphenicol	**Anti-microbial**	Tzelepi et al. 2010 [14]	Greece	0.016-8 ug/ml	3.6	46.5	49.9
Erthromycin	**Macrolide**	Tzelepi et al. 2010 [14]	Greece	0.016-6 ug/ml	10.2	43.6	46.0
Gentamacin	**Amino-glycoside**	Pederson et al. 2016 [15]	Greenland	1.5-4.0 mg/L	100	0	0
Penicillin	**Beta-lactam**	De Vries et al. 2009 [17]	the Netherlands	>0.2 ug/ml	NA	NA	16.5
		Tzelepi et al. 2010 [14]	Greece	0.064-2 ug/ml	4.3	64.1	27.7
		Regnath et al. 2016 [13]	Germany	0.002-32 mg/L	9.4	65.0	25.6
		Kovari et al. 2013 [16]	Switzerland	>1.0 L	NA	NA	22.8
		Salmeron et al. 2020 [12]	Spain	0.002-32 mg/L	6.8	73.1	20.1

Antibiotic	Class of antibiotics	Study	Location	MIC range	EUCAST		
					Susceptible (%)	Intermediate (%)	Resistant (%)
Tertacycline	**Protein synthesis inhibitor**	Tzelepi et al. 2010 [14]	Greece	0.25-2 ug/ml	12.8	56.7	24.2
		Pederson et al. 2016 [15]	Greenland	0.064-0.75 mg/L	79	21	0
		Regnath et al. 2016 [13]	Germany	0.016-256 mg/L	31.1	20.5	48.4
		De Vries et al. 2009 [17]	the Netherlands	>2.0 ug/ml	NA	NA	21.5
Spectinomycin	**Amino-cyclitol amino-glycosides**	Tzelepi et al. 2010 [14]	Greece	0.064-24 ug/ml	100	0	0
		Regnath et al. 2016 [13]	Germany	1-32 mg/L	100	0	0
		Pederson et al. 2016 [15]	Greenland	4-12 mg/L	100	0	0
		Salmeron et al. 2020 [12]	Spain	1.5-64 mg/L	100	0	0

Azithromycin

Data for Azithromycin was obtained from five studies. In Germany, the susceptibility of *Neisseria gonorrhea* isolates toward azithromycin was recorded as 73.5%, and resistance as 5.5% with 21.0% intermediate susceptibility in the period of 2004-2015. In the Netherlands, susceptibility of *Neisseria gonorrhea* isolates toward azithromycin was recorded as 90.1%, and resistance as 1.3% with 8.7% intermediate susceptibility in the period of 2012-2015. In another study from the Netherlands, no data was provided for susceptibility. Nevertheless, the same study with 11768 isolates (MIC range of 0.0-1 mg/L) provided that the intermediate susceptibility percentage in the isolates from men was 0.8%, in women was 0.9%, and in homosexual men was 2.0%, while resistance in the isolates from men was 2.5%, in women as 2.9% and in homosexual men was 5.7% in the period of 2007 to 2015. However, in Greenland, the susceptibility of *Neisseria gonorrhea* isolates toward azithromycin was 100% in 102 isolates having a MIC range of 0.023-0.125 mg/L. In Spain, of 2036 isolates (MIC range of 0.016-256 mg/L), 97.4% were susceptible to azithromycin, whereas 2.6% showed resistance in the period of 2013 to 2017.

Cefixime

Data for cefixime was obtained from three studies. In Germany, from 2004 to 2015, the susceptibility of *Neisseria gonorrhea* isolates toward cefixime was 100%. Whereas, in Spain, 95.1% of *Neisseria gonorrhea* isolates displayed susceptibility toward cefixime and 4.9% of isolates displayed resistance toward cefixime in the period of 2013-2017. In Switzerland, of 210 isolates, only 11.1% showed intermediate susceptibility toward cefixime in the period between 2005 and 2012.

Ceftriaxone

Data for ceftriaxone was obtained from six studies. In Germany, in the years from 2004 to 2015, of 434 isolates (MIC range of 0.002-0.125 mg/L), 100% of *Neisseria gonorrhea* isolates displayed susceptibility toward

ceftriaxone. Similarly, in Greenland, of 102 isolates (MIC range of 0.002-0.006 mg/L), the study recorded 100% susceptibility of *Neisseria gonorrhea* isolates toward ceftriaxone. In the Netherlands, 92% of isolates were susceptible to ceftriaxone while 8% showed intermediate susceptibility in the period of 2012-2015. Another study in the Netherlands showed 0% of isolates were resistant toward cefriaxone, while 1.2% of isolates from men, 2.4% of isolates from women, and 3.9% of isolates from homosexual men displayed intermediate susceptibility in the period of 2007-2015. In Spain, 99.7% of the isolates were susceptible, and only 0.3% were resistant to ceftriaxone having a MIC range of 0.016-0.38 mg/L from 2013 to 2017. However, in Switzerland, in the period between 2005 and 2012, only 3.5% of the isolates were intermediately susceptible to ceftriaxone.

Ciprofloxacin

Data for ciprofloxacin was obtained from five studies. In Germany, 29% of *Neisseria gonorrhea* isolates were susceptible, 0.2% of isolates were intermediately resistant and 70.3% of the isolates were completely resistant to ciprofloxacin. In the Netherlands, 44.4% of the isolates were resistant to ciprofloxacin. In Greece, 51.7% of *Neisseria gonorrhea* isolates were susceptible and 48.0% of the isolates were resistant to ciprofloxacin. In Spain, 48.6% of the isolates were susceptible, and 51.3% of the isolates were resistant to ciprofloxacin. While in Switzerland there was no information regarding susceptibility and intermediate resistance, 69.0% of *Neisseria gonorrhea* isolates were found to be resistant toward ciprofloxacin.

Cefotaxime

Data for cefotaxime was gathered from only two studies. In Greece, of 635 isolates, 7.5% showed susceptibility and only 0.3% of the isolates displayed resistance toward cefotaxime. In the Netherlands, out of 11,768 isolates, 2.8% of the isolates from men, 3.0% of the isolates from women, and 5.5% of the isolates from homosexual men displayed resistance against cefotaxime.

Chloramphenicol

Only one study provided data about chloramphenicol. In Greece, out of 653 isolates, 49.9% showed resistance toward chloramphenicol, while 46.5% displayed intermediate susceptibility, and only 3.6% of isolates remained susceptible to chloramphenicol.

Erythromycin

Only one study from Greece provided the data on erythromycin. The study showed that 46.0% of the isolates were resistant, 43.6% of the isolates were intermediately susceptible, and only 10.2 % of the isolates were susceptible against erythromycin.

Gentamicin

In Greenland, of 102 isolates, 100% of isolates displayed susceptibility toward gentamicin in the period of 2012-2015.

Penicillin

Data for penicillin was gathered from five studies. In the Netherlands, 16.5% of the isolates showed resistance and the data on susceptibility and intermediate susceptibility was not provided. However, in Greece, 64.1% of the isolates displayed intermediate susceptibility, 27.7% of the isolates showed resistance, and only 4.3% showed

susceptibility toward penicillin. In Germany, 65.0% of the isolates showed intermediate susceptibility, 25.6% of the isolates showed resistance and only 9.4% of the isolates exhibited susceptibility. Furthermore, at 73.1%, Spain recorded the highest percentage of intermediate susceptibility, while 2.1% were resistant and 6.8% of the isolates were susceptible. A study from Switzerland reported 22.8% of isolates were resistant to penicillin.

Tetracycline

Four studies provided data on tetracycline. In Greece, out of 635 isolates, 24.2% displayed resistance, 56.7% showed intermediate susceptibility, and only 12.8% of isolates were susceptible to tetracycline. In Greenland, 79% of isolates showed susceptibility, 0% showed resistance and 21% showed intermediate susceptibility toward tetracycline. However, in Germany, resistance was the highest in comparison to other studies: 48.4% of the isolates showed resistance, 20.5% displayed intermediate susceptibility and 31.1% of the isolates were susceptible to tetracycline. In the Netherlands, 21.5% of the isolates were recorded as resistant to tetracycline.

Spectinomycin

Data on spectinomycin was provided by four studies: in Greece, Germany, Greenland, and Spain. In all the studies, there was 100% susceptibility of *Neisseria gonorrhea* isolates toward spectinomycin having a MIC range of 0.064-24 ug/ml, 1-31 mg/L, 4-12 mg/L, 1.5-64 mg/L respectively.

Discussion

This systematic review has demonstrated the trends of susceptibility and resistance of *Neisseria gonorrhea* against different antibiotics in different regions of the EU/EEA/European region including Greenland. Interestingly, two studies from the Netherlands [17,19] gathered data on the homosexual population. These studies compared the resistance and susceptibility of *Neisseria gonorrhea* among homosexual men with that of the heterosexual population. It has been observed that homosexual men were more vulnerable to the development of antibiotic resistance against gonorrhea as compared to the heterosexual population. There can be various reasons for this. One of the reasons might be that the rate of *Neisseria gonorrhea* is higher among homosexual men than in the heterosexual population, which may lead homosexual men to have frequent treatment with antibiotics. This frequent exposure to antibiotics may lead to the adaptation of *Neisseria gonorrhea* to antibiotics. In addition to this, unique behaviors such as long-time asymptomatic development of infection may possibly be factors in the formation of antibiotic resistance in homosexual men [20]. Nevertheless, more research is needed to confirm these hypotheses.

This study also found different antibiotic resistance trends based on the type of antibiotics. In the case of ciprofloxacin, the proportion of isolates observed in five countries (the Netherlands, Greece, Germany, Switzerland and Spain) demonstrated that *Neisseria gonorrhea* has developed the highest resistance against ciprofloxacin, while the proportion of isolates for penicillin in same five countries showed that *Neisseria gonorrhea* developed the highest intermediate susceptibility toward penicillin. All the isolates of *Neisseria gonorrhea* from four countries (Germany, Greece, Spain and Greenland) remained 100% susceptible to spectinomycin, which makes it a highly effective treatment against *Neisseria gonorrhea*. Additionally, azithromycin, cefixime, and ceftriaxone also showed a high rate of susceptibility across different nations that maintains their effectiveness against *Neisseria gonorrhea* infection.

Furthermore, it has been observed that *Neisseria gonorrhea* isolates in Greenland had the highest susceptibility rate to antibiotics in comparison to other countries. For example, in the isolates in Greenland there was 0% antibiotic resistance, and intermediate susceptibility among the population residing in Greenland

toward azithromycin, ceftriaxone, and spectinomycin, whereas, 21% of the isolates demonstrated intermediate susceptibility and 0% resistance was observed toward tetracycline. The reason behind the success of antibiotics in Greenland is unclear as there is very little research on it, although the rate of *gonorrhoeae* infection is high in Greenland [15].

Nevertheless, a pattern of gradual increase of resistance among *Neisseria gonorrhea* against different antibiotics is evident in this study. The main reason behind growing antibiotic resistance among *Neisseria gonorrhea* is the ability of the bacteria to adapt and mutate to develop its defense system against commonly-used antibiotics [21]. Hence, it is crucial to make people aware of the consequences of the misuse of antibiotics. This awareness should extend beyond medical practitioners to the general population. For example, the use of antibiotics for animals on dairy and poultry farms is also common. This antibiotic treatment for dairy animals passes to the dairy products such as eggs, milk, etc., as well as other food products, such as meats [22]. As well, animals excrete antibiotics through urine and this antibiotics-laden urine enters the groundwater and pollutes it [23]. Hence, while there is an increasing focus on minimizing the use of antibiotics in a variety of venues, we tend to forget that humans consume antibiotics through indirect methods such as eating antibiotics-contaminated dairy and other animal products. Such collective incidences help bacteria adapt and develop defenses against available antibiotics.

Another reason for bacteria to adapt to antibiotics is frequent exposure to bacterial infections. This also applies to the infection of gonorrhoeae induced by the bacteria *Neisseria gonorrhea*. The main mode of transmission of *Neisseria gonorrhea* from one human to another human is unsafe sexual contact. Therefore, to minimize the antibiotic resistance of *Neisseria gonorrhea*, the public, medical practitioners and policymakers need to work together to protect public health from enabling the growth of antibiotic resistance in *Neisseria gonorrhea*. The general population shall also be educated by emphasizing the use of safe sex methods such as condoms. There is an additional necessity of developing public awareness, through educational programs, the promotion of preventive measures such as safe sex, and training healthcare workers to provide non-judgmental behavioral counseling. In the public awareness programs, health promotors should focus on educating people of all ages about antibiotic and antimicrobial resistance, encourage people to have sexually transmitted infection screening tests from time to time, and promote safe sex methods among all populations.

Additionally, to make the surveillance system more effective, it is also the time to observe the travel-related *Neisseria gonorrhea* infection trend. Due to technological advancements, it has been easy to travel from one continent to another continent of the world in a matter of hours. Thus, international travel plays an important role in importing different kinds of infections into different countries [24]. A surveillance system to monitor this phenomena has already been implemented in Nordic countries, where most of the *Neisseria gonorrhea*-acquired infections were related to international travel [25].

Furthermore, some preventive measures can also require policy changes. For example: screening the partner of a person who acquired gonorrhea, and investing in the invention of new effective and affordable antibiotics, and implementing rapid testing and contact tracing in the case of gonorrhea. This can assist surveillance in case of infection acquired during travel and track the antimicrobial bacterial strains, which can further help to protect the population.

Strengths of the study

The study narrowly assessed the literature elucidating trends of antibiotic resistance of *Neisseria gonorrhea* in different EU/EEA/European region countries within different timelines. This review is the first systematic review that synthesizes the data on the trends of antibiotic resistance of *Neisseria gonorrhea* within the EU/EEA/European region.

Limitations of the study

The study was unable to synthesize the data from each EU/EEA/European region country because only a limited number of studies have reported trends of antibiotic resistance of *Neisseria gonorrhea*. Therefore, there is a lack of synthesized data from all the EU/EEA/European region countries.

Conclusions

While some antibiotics are highly effective against gonorrhea infection, it is possible that with time they may lose their effectiveness. In the EU/EEA/European region, every country has different rates of susceptibility, intermediate susceptibility and resistance, hence it is essential to strengthen the surveillance and monitoring system by integrating public awareness and policy change in the surveillance process to keep treatment effective and public health protected.

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