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Antimicrobial Susceptibility Survey of Invasive *Neisseria meningitidis*, United States 2012–2016

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Abstract

Background.—Historically, antimicrobial resistance has been rare in US invasive meningococcal disease cases.

Methods.—Meningococcal isolates (n = 695) were collected through population-based surveillance, 2012–2016, and national surveillance, 2015–2016. Antimicrobial susceptibility was assessed by broth microdilution. Resistance mechanisms were characterized using whole-genome sequencing.

Results.—All isolates were susceptible to 6 antibiotics (cefotaxime, ceftriaxone, meropenem, rifampin, minocycline, and azithromycin). Approximately 25% were penicillin or ampicillin intermediate; among these, 79% contained mosaic *penA* gene mutations. Less than 1% of isolates were penicillin, ampicillin, ciprofloxacin, or levofloxacin resistant.

Conclusions.—Penicillin- and ampicillin-intermediate isolates were common, but resistance to clinically relevant antibiotics remained rare.

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Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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Keywords

Neisseria meningitidis ; invasive meningococcal disease; antibiotic resistance; penicillin; ciprofloxacin; antimicrobial susceptibility; *penA*

Neisseria meningitidis is a gram-negative diplococcus that causes life-threatening invasive meningococcal disease (IMD). Even though IMD incidence has declined in the United States since 2005, it remains an important public health concern due to its high morbidity and mortality; during 2012–2016, the average annual IMD incidence was 0.14 cases per 100 000 population, with a case fatality ratio of 15.9% (Centers for Disease Control and Prevention [CDC] unpublished). US IMD cases are predominantly caused by 3 of the 12 characterized *N. meningitidis* serogroups (B, C, and Y) [1] and multiple vaccines are available and recommended for meningococcal disease prevention [2].

Antibiotic treatment is important for both the management and prevention of IMD. Suspected IMD is treated empirically with cefotaxime or ceftriaxone (third-generation cephalosporins) and once the case is confirmed, treatment options include cefotaxime, ceftriaxone, penicillin G, or ampicillin [2]. However, susceptibility to penicillins should be confirmed prior to use [3]. To help prevent transmission, close contacts of IMD patients receive antibiotic prophylaxis, typically with ciprofloxacin, rifampin, or ceftriaxone [2]. In addition, individuals using complement inhibitors, such as eculizumab or ravulizumab, are sometimes recommended to receive penicillin as a long-term chemoprophylaxis option for IMD [4].

Although uncommon in the United States [3-6], multiple reduced antimicrobial susceptibility phenotypes and resistance mechanisms have been characterized within *N. meningitidis*. Resistance to third-generation cephalosporins has been infrequently reported and, to date, has not been confirmed (see an alert from the Instituto Costarricense de Investigación y Enseñanza en Nutrición y Salud and discussion in the *Journal of Clinical Microbiology* on a report by Manchanda and Bhalla [7-9]); additionally, an increased minimum inhibitory concentration (MIC) was observed in isolates containing allele 327 of the *penA* gene, which encodes penicillin-binding protein 2 [10]. Mosaic alleles in the *penA* gene that result in 4 or 5 amino acid substitutions (A510V, N512Y, I515V, H541N, I566V) have also been shown to cause intermediate susceptibility to penicillins [11]. β-lactamase–independent mechanisms of penicillin resistance are poorly understood but a penicillin-resistant clonal complex 23 (CC23) *N. meningitidis* strain containing the ROB-1 β-lactamase gene (bla_{ROB-1}) was recently characterized and has been detected in several countries [5]. Resistance to the chemoprophylaxis agents including rifampicin, caused by mutations in *rpoB* [12], and ciprofloxacin, caused by mutations in *parC* or the quinolone resistance determining region (QRDR) of *gyrA* [13, 14], have also been described.

The most recent phenotypic antimicrobial resistance (AMR) survey for *N. meningitidis* in the United States assessed isolates collected during 4 years: 2004, 2008, 2010, and 2011 [6]. Here, we conducted an AMR survey of bacterial isolates collected during 2012–2016 from IMD cases in the United States; susceptibility to 11 antibiotics was assessed using broth microdilution and the genetic mechanisms of resistance were investigated.

METHODS

Case Definition and Isolate Collection

A confirmed IMD case in the United States was defined as isolation of *N. meningitidis* by culture or detection of *N. meningitidis* by polymerase chain reaction (PCR) from a normally sterile body site (according to the Council of State and Territorial Epidemiologists case definition [15]). Epidemiologic information on all US IMD cases was submitted to the CDC through the National Notifiable Diseases Surveillance System. This study was reviewed by CDC and determined to be public health evaluation; patient consent and institutional review board review was not required.

Meningococcal isolates were submitted to the CDC through 2 domestic surveillance programs, including Active Bacterial Core Surveillance (ABCs) from 2012 to 2016 and Enhanced Meningococcal Disease Surveillance (EMDS) from 2015 to 2016. ABCs is an active, population- and laboratory-based surveillance system for invasive bacterial pathogens of public health importance and includes 10 catchment areas that cover approximately 44.2 million US residents (range, 13.6%–13.7% of the population during 2012–2016). As of 2016, EMDS included 45 state and 3 large jurisdiction health departments (including the 10 catchments areas within ABCs), resulting in 98% of the US population under surveillance. During 2015–2016, 535 (74.6%) of 717 confirmed cases included in EMDS had isolates submitted to CDC; among these, 508 were available for inclusion in this antimicrobial susceptibility survey.

Laboratory Characterization of *N. meningitidis* Isolates

N. meningitidis serogroup was characterized by multiple laboratory methods including real-time PCR, slide agglutination, and whole-genome sequencing as described previously [1]; each isolate genome was characterized using standard molecular typing methods (multilocus sequence typing and typing of PorA and FetA). As described previously [5], genes involved in antibiotic resistance were identified using an in-house bioinformatics pipeline that utilized a BLAST search of genome assemblies using reference sequences; amino-acid mutations were identified by aligning the translated sequence.

Antimicrobial Susceptibility Testing

Meningococcal isolates were tested by broth microdilution in accordance with the Clinical and Laboratory Standards Institute guidelines; susceptibility interpretations were assigned according to M100, 30th edition [16]. Customized lyophilized microdilution panels (Thermo Scientific Sensititre) were used and contained the following antimicrobial dilution series (μg/mL): cefotaxime (0.06–4), trimethoprim-sulfamethoxazole (0.06/1.19–4/76), minocycline (0.25–4), ciprofloxacin (0.015–4), rifampin (0.25–4), levofloxacin (0.015–8), ampicillin (0.06–16), azithromycin (0.25–4), ceftriaxone (0.06–8), meropenem (0.12–4), and penicillin G (0.03–8). Two quality control strains, *Streptococcus pneumoniae* ATCC 49619 and *Escherichia coli* ATCC 25922, were also included during testing. Isolates that were resistant to penicillin by broth microdilution were also assessed for β-lactamase activity by nitrocefin testing (BD BBL DrySlide). Significant changes in susceptibility between time periods were calculated using χ^2 statistics.

RESULTS

Meningococcal isolates collected during 2012–2016 from ABCs (n = 312; Table 1) and 2015–2016 from EMDS (n = 508; Table 2 and Supplementary Table 1) were assessed for susceptibility to 11 antibiotics. Isolates from both surveillance systems had a similar serogroup distribution, with serogroups B, C, and Y accounting for 80.4% and 80.5% of isolates in ABCs and EMDS, respectively (Supplementary Table 2).

All tested isolates were susceptible to 6 antibiotics assessed (cefotaxime, ceftriaxone, meropenem, rifampin, minocycline, and azithromycin); multiple reduced susceptibility patterns were observed for ampicillin, penicillin G, ciprofloxacin, levofloxacin, and trimethoprim-sulfamethoxazole (Table 1 and Table 2). The majority of isolates (ABCs, n = 201, 64.4%; and EMDS, n = 282, 55.5%) were resistant to trimethoprim-sulfamethoxazole, an antibiotic not currently recommended for IMD treatment [2]. Few isolates were resistant to other antibiotics; among the 695 isolates collected 2012–2016, ≤ 6 isolates (0.9%) were ampicillin, penicillin, ciprofloxacin, or levofloxacin resistant. Intermediate susceptibility was primarily observed for penicillin G (ABCs, n = 82, 26.3%; and EMDS, n = 160, 31.5%) and ampicillin (ABCs, n = 82, 26.3%; and EMDS, n = 147, 28.9%), with only a few isolates with intermediate susceptibility to other antibiotics identified (Table 1 and Table 2). When comparing ABCs isolates with reduced susceptibility by year, no clear changes in susceptibility were observed during 2012–2016 (Supplementary Table 3).

The reduced susceptibility to penicillin G was predominantly due to detection of 208 penicillin-intermediate isolates; only 6 penicillin-resistant isolates were identified. Year to year variation in the percent of penicillin G-intermediate isolates occurred, but no significant trends were detected ($P > .70$; Supplementary Table 4); the highest percentages were detected in 2015 and the lowest in 2013 (ranges 21.4%–30.8% for ABCs 2012–2016 and 28.9%–34.1% for EMDS; Supplementary Table 4). Comparable variation was observed for ampicillin-intermediate isolates (Supplementary Table 4). Among the 208 penicillin-intermediate isolates identified, 164 (78.8%) had at least 4 of the well-characterized mutations associated with mosaic *penA* alleles (F504L, A510V, I515V, H541N, or I566V; Supplementary Table 5) [11]. The *penA* 327 allele was only detected in 1 isolate (MICs, cefotaxime = 0.12 μg/mL and ceftriaxone ≤ 0.06 μg/mL), which was collected in 2016 and belonged to serogroup C, sequence type (ST)-11, CC11, with P1.5-1,10-8, and F1-5 (Supplementary Table 5).

In contrast to penicillin-intermediate isolates, penicillin-resistant isolates were rare. Two contained the bla_{ROB-1} gene (Supplementary Table 1), were resistant to both penicillins tested (MICs, 16–> 16 μg/mL for ampicillin and > 8 μg/mL for penicillin), were collected during 2015–2016 through EMDS, and belonged to the previously characterized β-lactamase–producing CC23 strain [5]. The 4 additional penicillin-resistant isolates (MIC = 0.5 μg/mL) were each collected during a different year, were β-lactamase–negative, and ampicillin-intermediate (MIC range, 0.5–1 μg/mL), and contained previously characterized mosaic *penA* gene mutations. Five of the 6 penicillin-resistant isolates were also trimethoprim-sulfamethoxazole resistant; isolates were susceptible to all other antibiotics tested.

Reduced susceptibility to fluoroquinolones was also rare within the isolates collected during 2012–2016. Three ciprofloxacin- and levofloxacin-resistant isolates were collected from 3 different states; these isolates were previously reported in a published genomics screen for *gyrA*-mediated ciprofloxacin-resistance [5]. Two of these resistant isolates (MIC ranges, ciprofloxacin 0.12–0.25 μg/mL and levofloxacin 0.25 μg/mL), collected through ABCs, were ST-2533 (CC23), had a T91I mutation within the *gyrA*-QRDR, and were also trimethoprim-sulfamethoxazole resistant. The third resistant isolate (MIC = 4 μg/mL for ciprofloxacin and levofloxacin), collected through EMDS, was ST-11 (CC11), had multiple mutations associated with reduced susceptibility to fluroquinolones (T91I, D95N, and T173A in *gyrA*; S87I in *parC*) and had reduced susceptibility to 3 other antibiotics assessed: the isolate was penicillin- and ampicillin-intermediate (MIC = 0.25 μg/mL for ampicillin and penicillin) and trimethoprim-sulfamethoxazole resistant. An additional 4 ciprofloxacin-intermediate and 2 levofloxacin-intermediate isolates were detected; among these, only 1 isolate was intermediate for both antibiotics and it was the only isolate that contained a mutation associated with reduced susceptibility to fluoroquinolones (*gyrA* D95N).

DISCUSSION

Phenotypic AMR surveys of isolates collected from US IMD cases, along with genetic investigations into the mechanisms of resistance, are important for ensuring that current antibiotic treatment and prophylaxis recommendations remain relevant. Here, we assessed *N. meningitidis* isolates collected during 2012–2016 for susceptibility to 11 antibiotics and demonstrated that resistance to clinically relevant antibiotics remained rare. However, reduced susceptibility mechanisms can be sustained within the US *N. meningitidis* population, which was demonstrated by the observations that more than half of isolates were trimethoprim-sulfamethoxazole resistant and more than a quarter were penicillin intermediate and ampicillin intermediate.

The US trends in *N. meningitidis* susceptibility can be assessed by comparing the 2012–2016 ABCs isolate susceptibility to the previous study that analyzed ABCs isolates from 2004 to 2011 [6]. Overall, the findings for the 5 antibiotics assessed by both studies were consistent: reduced susceptibility to rifampin, azithromycin, ciprofloxacin, and ceftriaxone was rare or not detected, but penicillin-intermediate isolates were more common. However, the percentage of penicillin-intermediate isolates has increased over time ($P < .0001$ when comparing 2004–2011 vs 2012–2016); 8.0%–16.7% of 2004–2011 isolates were penicillin intermediate during each year assessed compared to 21.4%–30.8% in 2012–2016. The increased proportion of US penicillin-intermediate isolates during 2012–2016 is consistent with global trends, as multiple countries have reported an increased proportion of penicillin-intermediate isolates since 2000 [17-20].

The clinical significance of the increased penicillin-intermediate and the 4 β-lactamase–negative, penicillin-resistant isolates identified in this study remains unclear. An extended medical record review of ABCs cases in 2009 demonstrated that penicillin was not commonly used for treatment of US IMD; furthermore, no patients in this review were exclusively treated with penicillin [21]. Additionally, recent identification of the β-lactamase–producing serogroup Y CC23 strain resulted in a recommendation that

susceptibility to penicillins should be confirmed prior to use for IMD treatment [3]. However, the increased penicillin-intermediate isolates could still pose a concern for individuals being treated with complement inhibitors, who sometimes receive long-term penicillin prophylaxis. Finally, the clinical significance of the 4 β-lactamase–negative, penicillin-resistant isolates with MICs values within 1 or 2 dilutions of the intermediate breakpoint (0.5–1 μg/mL) remains unknown; an in vivo mouse model study concluded that meningococcal infections caused by strains exhibiting an MIC of 0.5 μg/mL were treatable [22].

Inclusion of the susceptibility results of isolates collected during 2015–2016 through EMDS resulted in multiple important observations. First, the susceptibility patterns observed among both surveillance programs were similar, demonstrating that the findings from the ABCs surveillance program may be representative of the national trends during the study period, even though the number of isolates collected each year was low. In addition, inclusion of the EMDS isolates increased the number of isolates that could be assessed in 2015–2016 (n = 125 from the ABCs catchment areas with an additional n = 383 from other jurisdictions), which led to improved detection of uncommon, novel susceptibility phenotypes; for example, the 2 novel β-lactamase–producing CC23 strain isolates were successfully detected through EMDS jurisdictions outside of the ABCs catchment areas, showing the importance of the nation-wide surveillance. Finally, having comprehensive national susceptibility data for 2015–2016 (EMDS) will serve as an important baseline for future studies, which will likely involve a comprehensive analysis of nation-wide US *N. meningitidis* susceptibility trends.

Overall, this 2012–2016 survey demonstrated that, with the exception of penicillin-intermediate isolates, the US *N. meningitidis* population remained susceptible to clinically relevant antibiotics. The increasing penicillin-intermediate *N. meningitidis* population observed and the detection of the novel β-lactamase–producing, penicillin- and ciprofloxacin-resistant strain in 2019–2020 [3, 5], highlight the continued importance of *N. meningitidis* AMR surveillance in the United States to monitor trends, paired with genotypic investigations to understand the underlying mechanisms of resistance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments.

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Table 1.

Antimicrobial Susceptibility of Isolates From Invasive Meningococcal Disease Cases, Collected Through Active Bacterial Core Surveillance, United States, 2012–2016 (n = 312[a])

Antibiotic	S, n (%)	I, n (%)	R, n (%)	NS, n (%)	MIC Range, µg/mL	MIC50, µg/mL	MIC90, µg/mL
Ampicillin	230 (73.7)	82 (26.3)	0 (0)	NA	≤0.06–1	≤0.06	0.25
Penicillin	226 (72.4)	82 (26.3)	4 (1.3)	NA	≤0.03–0.5	≤0.03	0.12
Cefotaxime	312 (100)	NA	NA	0 (0)	≤0.06–0.12	≤0.06	≤0.06
Ceftriaxone	312 (100)	NA	NA	0 (0)	≤0.06–0.12	≤0.06	≤0.06
Meropenem	312 (100)	NA	NA	0 (0)	≤0.12	≤0.12	≤0.12
Ciprofloxacin	308 (98.7)	2 (0.6)	2 (0.6)	NA	≤0.015–0.25	≤0.015	≤0.015
Levofloxacin	310 (99.4)	0 (0)	2 (0.6)	NA	≤0.015–0.25	≤0.015	≤0.015
Rifampin	312 (100)	0 (0)	0 (0)	NA	≤0.25–0.5	≤0.25	≤0.25
Minocycline	312 (100)	0 (0)	0 (0)	NA	≤0.25–1	≤0.25	0.5
Azithromycin	312 (100)	0 (0)	0 (0)	NA	≤0.25–1	≤0.25	≤0.25
Trimethoprim-sulfamethoxazole	100 (32.1)	11 (3.5)	201 (64.4)	NA	≤0.06/1.19–>4/76	1/19	4/76

Abbreviations: I, intermediate; MIC, minimum inhibitory concentration; NA, not applicable (no Clinical Laboratory and Standards Institute breakpoint is defined for the specified susceptibility category); NS, nonsusceptible; R, resistant; S, susceptible.

[a]The number of isolates collected per year varied (2012 = 74, 2013 = 56, 2014 = 57, 2015 = 65, and 2016 = 60).

Table 2.

Antimicrobial Susceptibility of Isolates From Invasive Meningococcal Disease Cases, Collected Through Enhanced Meningococcal Disease Surveillance, United States, 2015–2016 (n = 508[a])

Antibiotic	S, n (%)	I, n (%)	R, n (%)	NS, n (%)	MIC Range, µg/mL	MIC50, µg/mL	MIC90, µg/mL
Ampicillin	360 (70.9)	146 (28.7)	2 (0.4)	NA	≤0.06–>16	≤0.06	0.25
Penicillin	344 (67.7)	160 (31.5)	4 (0.8)	NA	≤0.03–>8	0.06	0.25
Cefotaxime	508 (100)	0 (0)	0 (0)	0 (0)	≤0.06–0.12	≤0.06	≤0.06
Ceftriaxone	508 (100)	0 (0)	0 (0)	0 (0)	≤0.06–0.12	≤0.06	≤0.06
Meropenem	508 (100)	0 (0)	0 (0)	0 (0)	≤0.12	≤0.12	≤0.12
Ciprofloxacin	504 (99.2)	2 (0.4)	2 (0.4)	NA	≤0.015–4	≤0.015	≤0.015
Levofloxacin	504 (99.2)	2 (0.4)	2 (0.4)	NA	≤0.015–4	≤0.015	≤0.015
Rifampin	508 (100)	0 (0)	0 (0)	NA	≤0.25–0.5	≤0.25	≤0.25
Minocycline	508 (100)	0 (0)	0 (0)	NA	≤0.25–1	≤0.25	0.5
Azithromycin	508 (100)	0 (0)	0 (0)	NA	≤0.25–2	≤0.25	≤0.25
Trimethoprim-sulfamethoxazole	208 (40.9)	18 (3.5)	282 (55.5)	NA	≤0.06/1.19–>4/76	1/19	4/76

Abbreviations: ABCs, active core bacterial surveillance; EMDS, enhanced meningococcal disease surveillance; I, intermediate; MIC, minimum inhibitory concentration; NA, not applicable (no Clinical Laboratory and Standards Institute breakpoint is defined for the specified susceptibility category); NS, nonsusceptible; R, resistant; S, susceptible.

[a]EMDS included 45 state and 3 large jurisdiction health departments (including the 10 catchments areas within ABCs). A total of 125 isolates were collected from ABCs catchment areas during 2015–2016 and are shown in both Table 1 and Table 2. Supplementary Table 1 provides EMDS data for 2015 and 2016 by jurisdictions within and outside the ABCs catchment areas.