State-Based Surveillance to Determine Trends in Meningococcal Disease

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SYNOPSIS

Objectives. Meningococcal disease (MD), is a leading cause of meningitis in the U.S. The purpose of this study was to determine the epidemiology of MD in Oklahoma, including trends, high-risk populations, and outcomes.

Methods. Cases from the statewide passive reporting system with disease onset between 1988 and 2004 were included; 2002–2004 cases were linked to hospital discharge data. We performed a multivariate logistic regression of variables predicting death.

Results. There were 545 total cases (mean annual incidence rate 1.0/100,000); 13% died. Rates were highest for children younger than 2 years of age; black males had rates two times higher than the state rate and a different age distribution than other race-gender groups. Mean length of hospital stay was 12 days and mean charges were $37,724. For every 10 years of age, the risk of death increased 13% (adjusted odds ratio 1.13, 95% confidence interval [CI] 1.05, 1.22). People younger than age 40 who developed MD between October and February were 68% more likely to die than those who developed it in other months (rate ratio [RR] 1.68, 95% CI 1.39, 2.05); an increased risk of death during these months was not statistically significant in people aged 40 and older (RR 1.19, 95% CI 0.83, 1.69).

Conclusion. Using statewide public health surveillance data to characterize the epidemiology of MD is important to understand local trends and risk factors.

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Neisseria meningitidis (*N. meningitidis*), the organism that causes meningococcal disease (MD), is a leading cause of bacterial meningitis in the U.S.[1] The estimated number of cases nationally is 1,400 to 2,800 per year (annual incidence 0.5 to 1.1/100,000 population).[2] The MD case-fatality rate is 8% to 15% in treated cases, and significant sequelae, including neurological damage and hearing and limb loss, may occur in survivors.[3] The clinical spectrum of disease includes joint infections, pneumonia, meningitis, and fulminant septicemia.[4] Septicemia results in higher fatality than meningitis.[5]

High-risk populations for sporadic MD include the very young (those younger than 1 year), people who have deficiencies in the terminal common complement pathway,[6,7] and those with anatomic or functional asplenia.[8] Antecedent viral infection, factors promoting crowding (e.g., poverty, military barracks, and college dormitories), chronic underlying illness, as well as active and passive smoking have been found to be associated with increased risk of disease.[9–15] Black people and people of low socioeconomic status have higher rates of disease in the U.S.,[16,17] although these increases may be due to other risk factors.[18] College students in Britain and the U.S., particularly those living in dormitories, have been found to be at increased risk for disease.[19,20]

Although epidemic disease was once common in the U.S.,[21] less than 2% of cases in the U.S. now occur in outbreaks or clusters.[22] While outbreaks of MD are unusual, there is evidence that localized community- and organization-based outbreaks have occurred with greater frequency in the U.S. since the early 1990s,[23] and are associated with increased case-fatality rates.[2] An organization-based MD outbreak is defined as three or more confirmed or probable cases of MD during a period of three months or less in people who have a common affiliation but no close contact, resulting in ≥10 cases per 100,000 people. A community-based MD outbreak is defined as at least three confirmed or probable cases during a period of three months or less among people residing in the same area who are not close contacts and who do not share a common affiliation, with ≥10 cases per 100,000 population.[22]

Capsular and acapsular forms of meningococci exist. Only capsular forms, with 13 serologically distinct types, are routinely isolated from cases of invasive MD. Capsular types are designated as serogroups. While each serogroup is potentially epidemiologically distinct, the significance of these differences, if any, for the purposes of disease prevention and management is not yet well understood. In Oregon, the proportional change in incidence of serogroup B was found to herald the emergence of hyperendemic disease.[24] Group Y has recently become more common in the U.S. Differences in age-specific attack rates by serogroup are known to exist in the U.S. Among infants younger than 1 year, more than 50% are found to have serogroup B. In those aged 11 years or older, 75% have groups C, Y, or W-135.[23]

Because of increased awareness in recent years of the risk of MD in college dormitory residents, many state legislatures have considered mandating vaccination prior to college attendance. As of August 2005, nine states require proof of vaccination or a waiver for all incoming students and/or all incoming students residing on campus.[25] In Oklahoma, vaccination is required for incoming students residing in on-campus housing. In addition, 23 states require that college students residing on campus receive information on the risks associated with MD, and the risks, benefits, and availability of vaccine.

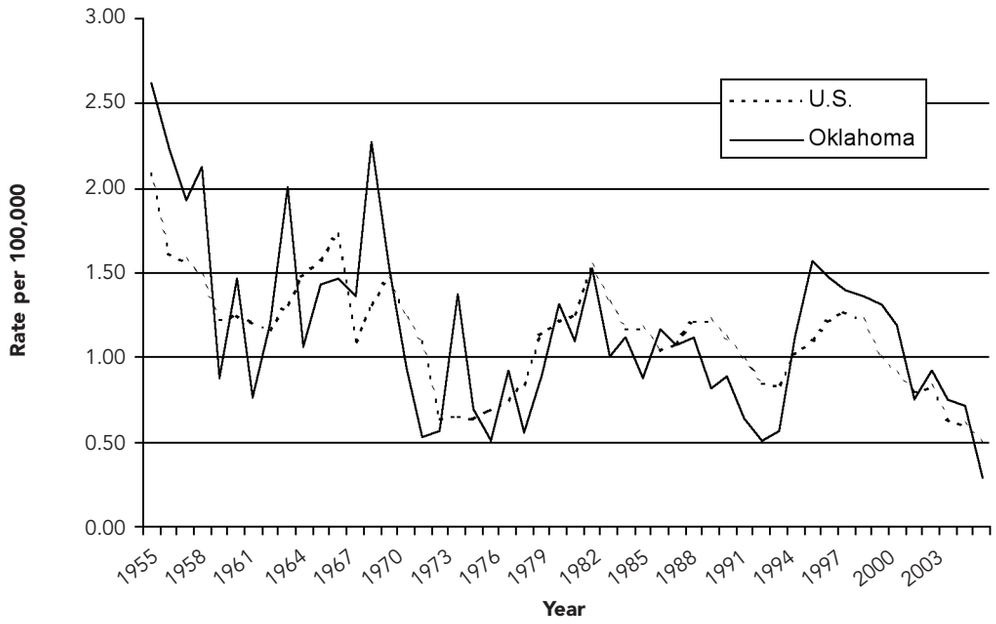
MD has been reportable in Oklahoma since the 1920s. Passive reporting of MD to the Oklahoma State Department of Health (OSDH) has occurred since that time. All clinical isolates of *N. meningitidis* from patients with MD are required to be submitted to the OSDH Public Health Laboratory for confirmation and serogrouping. Physicians, including the Office of the Chief Medical Examiner, and clinical and diagnostic laboratories are required to report cases of MD. Cases are investigated to determine the need for prophylactic chemotherapy among close contacts. Since 1955, rates of MD in Oklahoma and the U.S. have been similar and have declined more than 80%, although considerable fluctuations in disease incidence occurred during that time (Figure 1). The reasons for the large decline in disease incidence are not known; it is possible that antigenic shifts of *N. meningitidis* are responsible for disease fluctuations.[26]

The purpose of this study was to determine trends in MD, including high-risk populations and outcomes, in Oklahoma from 1988 to 2004.

METHODS

The case definition of MD in Oklahoma follows that of the Centers for Disease Control and Prevention and the Council of State and Territorial Epidemiologists.[27] Confirmed cases require isolation of *N. meningitidis* from a normally sterile site (i.e., blood, cerebrospinal fluid [CSF], or synovial, pleural, or pericardial fluid) along with clinically compatible symptoms such as meningitis, sepsis, or purpura fulminans. A probable case of MD is defined as a clinically compatible case that has a positive antigen test in CSF or clinical purpura fulminans in the absence of a positive blood culture.

Figure 1. Rates of meningococcal disease, U.S. and Oklahoma, 1955–2004



Suspect cases without positive confirmatory laboratory tests or symptoms are not counted as reportable cases and are excluded. Oklahoma residents with confirmed or probable MD with disease onsets between 1988 and 2004 were included in the study.

To ascertain the completeness of MD reporting, results of a 2003 laboratory audit were compared with OSDH records. Audited facilities included 83 of 118 (70.3%) acute care hospital laboratories and reference laboratories in Oklahoma. No unreported cases of MD were discovered by the audit. Death certificates coded International Classification of Diseases, Ninth Revision (ICD-9) 036.0–036.9 (1988 to 1999) and ICD, 10th Revision (ICD-10) codes A39.0–A39.9 (2000 to 2004) were reviewed. Sixty-six of 71 deaths (92.9%) attributable to MD had been previously reported.

Cases were categorized as urban if the county of residence was Oklahoma or Tulsa County; otherwise, they were coded rural. Meningococcal cases from 2002 to 2004 were linked with statewide hospital discharge data to determine length of stay, outcome, charges, and payors.

Data analysis and statistical testing were performed using SAS® Version 9.1.[28] Rates per 100,000 population were calculated using bridged race census estimates for Oklahoma for each year, from 1988 to 2004.[29] Fisher's exact test, relative risk, and 95% confidence intervals (CIs) were used to determine significant associations; significance was defined as $p<0.05$.

A logistic regression model testing predictors of death was constructed. Independent variables considered for inclusion in the model included age at onset, sex, race, serogroup, year and month of onset, urban vs. rural residence, and specimen source. To create a multivariate model, we first performed univariate analysis on each variable and retained those variables with $p<0.10$ using the Chi-square test. All the retained variables were considered in a multivariate model. We also assessed any potential interactions.

RESULTS

From 1988 to 2004, 545 cases of MD occurred in Oklahoma; 71 (13.0%) died. The number of cases ranged from 10 to 51 per year. The mean annual incidence rate during this time for Oklahoma and the U.S. was 1.0/100,000 population. The mean annual incidence rate from 2002 to 2004 (0.58) was 26.0% below the rate from 1988 to 1990 (0.78). One instance of secondary transmission in a household (two cases) occurred in 1992. One organization-based outbreak associated with a church occurred in 2000. Two confirmed cases and one probable case were associated with the cluster (age range 8 to 13 years, one female, two males). An isolate for serogrouping was available for one case, from which group C was identified. No deaths were associated with the outbreak. No community-based outbreaks were observed.

Age at onset ranged from <1 year of age to 99 years of age (mean 22.6 years, median 10 years). Infants younger than 1 year of age represented 18.2% of cases (annual rate 16.5/100,000) and nearly one-quarter occurred among children 0–23 months of age; the mean annual rate among children 0–23 months of age was significantly higher than among all other age groups (Table 1). Among people older than 14 years of age, adults aged 65 and older had a significantly higher incidence rate. The rate among males was 22.0% higher than among females (1.1 vs. 0.9 per 100,000, respectively) but was not statistically different. While the rate among people in urban areas was 22.0% higher than in rural areas, this was not statistically significant.

Data on race were available for 487 (89.4%) cases. The rate among black individuals (1.28/100,000) was significantly higher than among white individuals (0.91/100,000) and Native Americans (0.57/100,000). The rate among Native Americans was not significantly different from white individuals. One case occurred in a person of Asian race. White residents had the highest rates among children 0 to 4 years of age and people aged 65 years and older; black individuals had the highest rates in all other age categories (Figure 2). The rate among black males was significantly higher than among other race-gender groups (Table 1). Black males aged 4 years and older had the highest incidence of disease in all age groups and followed a different disease age distribution than the other race-gender groups; it was the only race-gender group in which rates increased in the 15–24 and 45–54 age groups and did not increase in the 65+ age group (Figure 2). However, individual cell sizes were too small to determine if this distribution was significantly different from other races.

Case-fatality rates (CFRs) varied from a high of 24.0% (six of 25) in 2003 to 3.9% (one of 26) in 1988. The five-year mean CFR from 1988 to 1992 was 11.1% as compared with 15.0% from 2000 to 2004; this difference was not statistically significant. People aged 40 years and older were 81% more likely to die than people younger than 40 years of age (rate ratio [RR] 1.81, 95% CI 1.18, 2.79). The CFR among rural cases was one-third higher than among urban cases, although it did not reach statistical significance (RR 1.33, 95% CI 0.74, 2.39).

Of 516 confirmed cases of MD, 115 (22.3%) did not have *N. meningitidis* isolates available for serogrouping at the OSDH laboratory. Of those that were provided to the OSDH laboratory, 122 (30.4%) were found to be serogroup B, 113 (28.2%) were serogroup C, 93 (23.2%) were serogroup Y, 15 (3.7%) were serogroup W-135, and one (0.3%) was serogroup X; 57 (14.2%) were not able to be grouped. Prior to 1993, serogroup Y had only been isolated once, while 33.3% of

Table 1. Meningococcal disease by outcome and selected demographic characteristics, Oklahoma, 1988–2004

Selected demographics	N *(percent of total)*[a]	*Rate/100,000 (95% CI)*	*Number died (percent of total)*	*Case fatality rate (percent)*[b]
Age range (in years)				
0–1	133 (24.4)	8.4 (6.9, 9.8)	16 (22.5)	12.0
2–14	134 (24.6)	1.3 (1.0, 1.5)	9 (12.7)	6.7
15–24	60 (11.0)	0.7 (0.5, 0.9)	7 (9.9)	11.7
25–39	49 (9.0)	0.4 (0.3, 0.5)	7 (9.9)	14.3
40–64	67 (12.3)	0.4 (0.3, 0.5)	13 (18.3)	19.4
≥65	102 (18.7)	1.4 (1.1, 1.7)	19 (26.8)	18.6
Race/gender				
White female	207 (38.0)	0.9 (0.8, 1.0)	29 (41.0)	14.0
White male	218 (40.0)	1.0 (0.8, 1.1)	26 (36.6)	11.9
Black female	18 (3.3)	0.8 (0.4, 1.2)	3 (4.2)	16.7
Black male	43 (7.9)	2.0 (1.7, 2.6)	7 (9.8)	16.3
Native American female	11 (2.0)	0.4 (0.2, 0.7)	3 (4.2)	27.3
Native American male	19 (3.5)	0.8 (0.4, 1.1)	0 (0.0)	0.0
Residence				
Urban[c]	231 (42.4)	1.2 (1.0, 1.3)	12 (16.9)	10.3
Rural	314 (57.6)	0.9 (0.8, 1.0)	59 (83.1)	13.8
Overall	545 (100.0)	1.0 (0.9, 1.0)	71 (100.0)	13.0

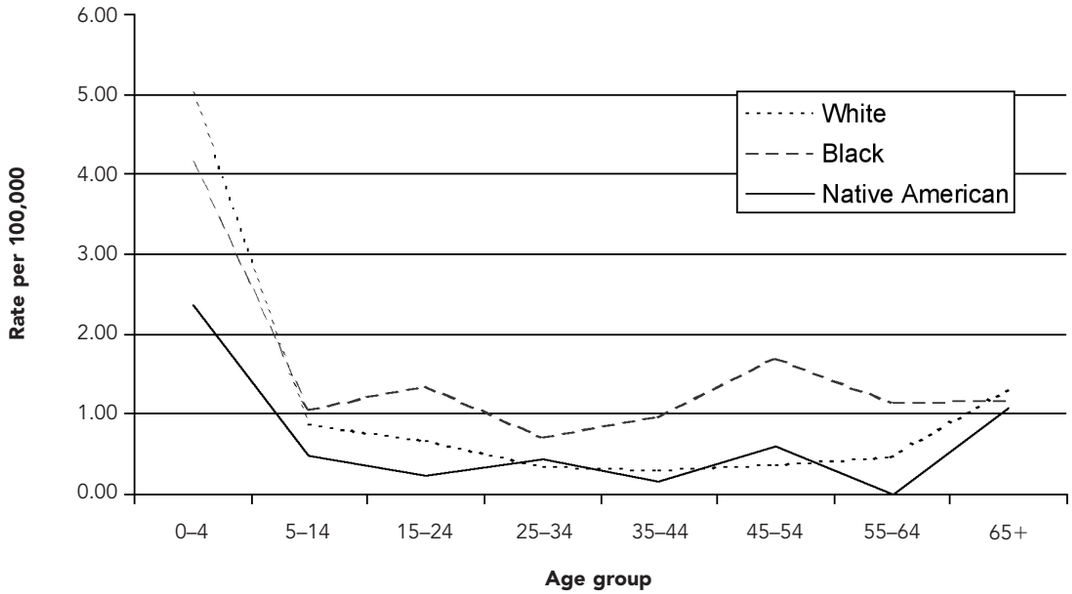
[a]Includes "outcome unknown"

[b]Number died/total cases (including outcome unknown) multiplied by 100

[c]Case subjects resided in Tulsa or Oklahoma County at time of onset.

CI = confidence interval

Figure 2. Rates of meningococcal disease by race and age group, Oklahoma, 1988–2004



isolates since 1994 were serogroup Y. No other shifts in serogroup were noted. Fatality rates by serogroup were W-135 (33.3%), Y (18.3%), C (15.0%), and B (10.7%). These differences did not reach statistical significance (Fisher's exact test comparing W-135 vs. others combined, p=0.059).

Among groupable isolates obtained between 1988 and 2004, 60.8% of infants younger than 2 years of age were found to have serogroup B, followed by C (24.1%), Y (7.6%), and W-135 (7.6%). Serogroup C was the most common serogroup in people aged 2 to 39 years (48.1%), followed by B (33.3%), Y (12.9%), and W-135 (2.7%). Among people aged 40 years and older, serogroup Y was found to be the most common (54.6%), followed by B (23.2%), C (17.6%), and W-135 (4.6%). No differences in serogroup were noted by sex or race.

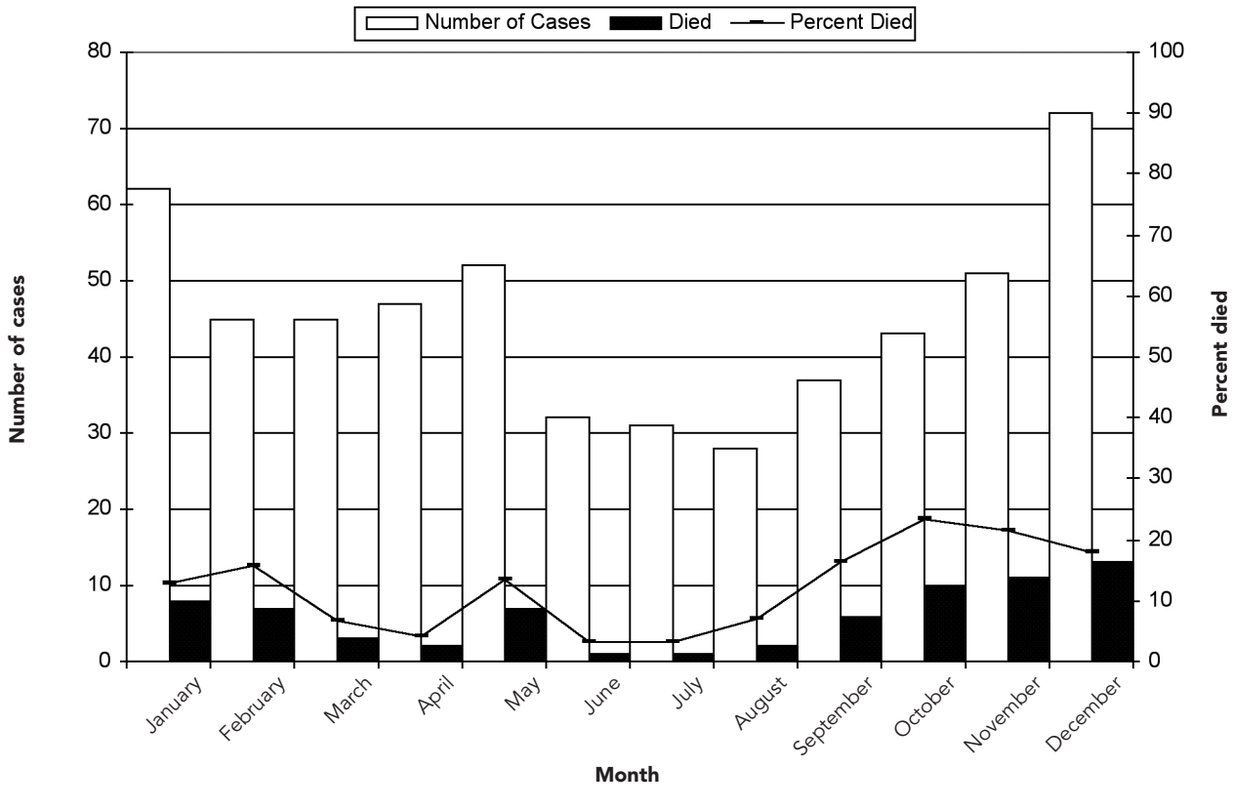
Forty-six MD cases matched with the hospital discharge database from 2002 to 2004. The mean length of hospital stay was 12 days (median eight days, range one to 128 days). Total hospital charges were more than $1.7 million. Mean hospital charges were $37,724 (median $18,393, range $776 to $269,367). Nearly three-quarters (72.0%) of people were discharged home, 11.0% were discharged to home health care, 7.0% died, 4.0% each were discharged to another acute care hospital or intermediate care facility, and 2.0% went to a rehabilitation center. Two people with meningococcemia and one person with Waterhouse-Friderichsen syndrome required amputations. Insurance was the primary payor for 44.0% of hospitalized people, followed by Medicaid (37.0%), self-pay (11.0%), Medicare (7.0%), and other government health care (2.0%).

Age and season of onset were the only variables found to predict death as an outcome measure in the logistic regression model. Race, sex, specimen source, year of onset, urban vs. rural residence, and serogroup were not found to be significant contributors for risk of death from MD. Older age at onset was associated with a higher likelihood of dying; for every 10 years of age, the risk of death increased 13.0% (adjusted odds ratio [AOR] 1.13, 95% CI 1.05, 1.22). Season of onset between October and February (Figure 3) was associated with greater risk of death than disease onset during the rest of the year (AOR 2.53, 95% CI 1.47, 4.33). Upon testing for interaction, the significance between age and season was 0.07. We then stratified our analysis by age $<$40 and $\geq$40 years. People younger than age 40 who developed MD between October and February (Figure 4) were 68.0% more likely to die than those younger than age 40 who became ill in other months (RR 1.68, 95% CI 1.39, 2.05); the increased risk of death during these months was elevated but not statistically significant in those aged 40 and older (RR 1.19, 95% CI 0.83, 1.69).

DISCUSSION

This study showed that MD continues to be an important cause of morbidity and mortality in Oklahoma.

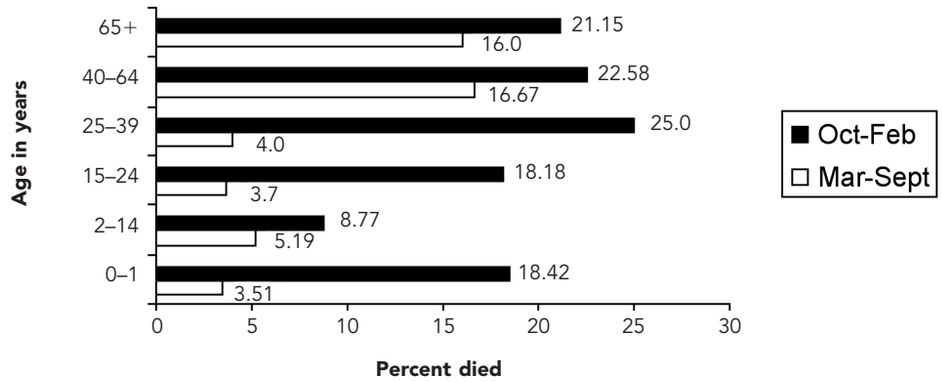
Figure 3. Meningococcal disease by month of onset and outcome, Oklahoma, 1988–2004



This is one of the first studies to link population-based surveillance data and hospital discharge data to evaluate severity measures such as length of stay, charges, discharge status, and outcomes. Approximately one-quarter of these hospitalized patients either died (7.0%) or were discharged to post-acute care facilities (17.0%). There were nearly $2 million in hospital charges in a three-year period and less than one-half of people had private insurance. These costs do not reflect the substantial financial burden from associated disabilities and follow-up care, lost wages, and years of productive life lost.

We are not aware of any studies that have correlated mortality with age and seasonality. The finding that the risk of death increases during winter months, particularly at younger ages, may be an important and

Figure 4. Meningococcal disease death rates by age group and season of onset, Oklahoma, 1988–2004



underappreciated risk factor for MD mortality. Increased incidence of MD following respiratory infection—such as with influenza, which has an increased incidence in winter—has been hypothesized by several researchers as a possible explanation for the observed disease seasonality.[9,12,30–32] Increased MD severity and mortality during the influenza season was reported by Hubert et al.,[32] although the seasonal difference in mortality did not reach statistical significance, and increased mortality was not noted in younger people.

While studies have shown that black people have a higher incidence of MD than their white counterparts,[2,33,34] our study found the racial disparity to be entirely attributable to black males. It is not currently possible to estimate an increased risk in black people due to biologic vs. socioeconomic risk factors. Further research is warranted to answer this question.

This study confirmed previous associations of increased risk of death with increasing age.[35] The lack of decline in the case-fatality rate over time is not unique to Oklahoma.[36] While the frequency of localized, organization- or community-based outbreaks has been increasing in the U.S. since the early 1990s, this trend was not observed in Oklahoma.

There are two meningococcal vaccines currently available in the U.S. (Table 2). Both are quadrivalent, offering protection against serogroups A, C, Y, and W-135. MPSV4 (Menomune), a polysaccharide vaccine, is licensed for use in people 2 years of age and older, and MCV4 (Menactra), a conjugate vaccine, may be used in those aged 11 to 55 years.

While immunization is an important component of MD prevention, it is clear that immunization alone cannot prevent a large proportion of cases, even if all eligible people received the vaccine. In both the U.S. and Oklahoma, serogroup B, which is not covered by either vaccine, causes 30.0% of cases, and 24.0% of Oklahoma cases occurred in people younger than 2 years of age (i.e., those not eligible for vaccination). While vaccination status of cases was unknown, only 55.0% of Oklahoma MD cases from 1988 to 2004 were of appropriate age for vaccination and were infected with meningococcal serogroups that could have been prevented by MPSV4 (Menomune); only one-quarter (27.0%) met both criteria for age and serogroup coverage in MCV4 (Table 2). The addition of serogroup B to the vaccine is an active area of research. Challenges to adding this serogroup include poor immunogenicity as well as structural similarities of potential group B antigens to human neural antigens, raising safety concerns.[37]

Limitations

There were some limitations in our research. We were unable to report data by infection type, as uniform clinical data were not collected. Due to small cell size, we could not calculate the statistical significance of race/sex groups by age. We also did not know the vaccination status of cases, limiting inferences regarding vaccine preventability. Finally, though this study confirmed substantial morbidity, mortality, and disability due to MD, it is possible that we undercounted cases when no culture or antigen tests were positive.

Table 2. Oklahoma meningococcal disease cases within age recommendations and with serogroups covered by the meningococcal vaccines

Vaccine	*Date vaccine available*	*Recommended age groups*	*Duration of immunity*	*Serogroups covered by vaccine*	*Number of Oklahoma MD cases, 1988–2004, in age groups recommended for vaccine (percent)*	*Number of Oklahoma MD cases, 1988–2004, with serogroup covered in vaccine (percent)*	*Number of Oklahoma MD cases, 1988–2004, both age-eligible and serogroup covered in vaccine (percent)*
MPSV4 (Menomune)	1981	≥2 years	Varies, probably ≥3 years in those <4 years of age; longer in older people	A, C, Y, W-135	265/344[a] (77)	221/344[a] (64)	190/344[a] (55)
MCV4 (Menactra)	January 2005	11–55 years	Unknown, presumed to be longer than MPSV4	A, C, Y, W-135	123/344[a] (36)	221/344[a] (64)	91/344[a] (27)

[a]Excludes 201 cases for whom serogroup information was not available.

MD = meningococcal disease

CONCLUSION

This study demonstrated the importance of using statewide population-based public health surveillance to characterize the state-specific epidemiology of MD, as state patterns may not reflect national trends.[38] We recommend other states assess their data using logistic regression analyses to determine if the mortality risk by age and season is similar to our findings of an increased risk of death in winter months among individuals of younger ages. Public health efforts in Oklahoma should include heightening awareness of the medical community and public regarding high-risk groups and the potential for vaccination, as well as symptomatology and the need for prompt assessment and treatment. Further research in Oklahoma should include an evaluation of the intrinsic or extrinsic risk factors of black males for MD.

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