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Neisseria meningitidis Epidemiology and Molecular Epidemiology in Atlanta, Georgia, 1989-2010

By

Qiuzhi Chang

Master of Science in Public Health

Department of Epidemiology

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David S. Stephens, MD

Faculty Thesis Advisor

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By

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B.Sc.H., Queen's University (CAN), 2010

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An abstract of

A thesis submitted to the Faculty of the
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Abstract

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By Qiuzhi Chang

Human infections due to the bacterial pathogen *Neisseria meningitidis* remain a serious health problem worldwide. We determined the incidence and epidemiologic characteristics of invasive disease due to *N. meningitidis* occurring in metropolitan Atlanta between 1989 and 2010. In addition, we addressed the geographical and temporal trends in the occurrence of invasive meningococcal disease and the spread of invasive clonal complexes over these two decades in the community. Cases of meningococcal disease that occurred in metropolitan Atlanta between 1989 and 2010 were identified through active prospective laboratory and population based surveillance. Genetic typing (MLST) was conducted on meningococcal isolates to identify clonal complexes and ArcMap10 was used to geocode US addresses in order to geographically study the invasive meningococcal cases. A total of 468 cases of invasive meningococcal disease were detected in the Atlanta surveillance area from 1989 to 2010. The incidence of meningococcal disease significantly declined since 2001 (χ^2 for linear trend, $p = 0.007$) and become more distributed geographically over time in the surveillance area. Genetic typing of clonal complex was available for 258 invasive meningococcal cases. Almost all of serogroups C and Y meningococcal disease were caused by the ST-11 complex and ST-23 complex, respectively, suggesting that closely related strains are circulating in the community and causing sporadic disease. In contrast, serogroup B meningococcal disease over the past twenty years were from multiple distinct genetic lineages. The temporal trends of *N. meningitidis* clonal complexes were reflected in the geographic distribution of meningococcal disease over time. Molecular characterization of meningococcal isolates is vital in determining the spread of specific clonal complexes in the community. In addition, it is important to conduct ongoing surveillance as the trends in the occurrence of meningococcal disease will affect future vaccine or other prevention strategies.

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Background

Human infections due to the bacterial pathogen *Neisseria meningitidis* remain a serious health problem worldwide. *N. meningitides* (the meningococcus) causes a spectrum of human diseases with a case fatality rate between 10% and 20%. The two most common clinical manifestations of the disease are rapid onset meningitis, or infection of the meninges and central nervous system, and meningococcemia, or severe sepsis. It is estimated that the meningococcus infects 1.2 million people and kills over 135,000 per year (1).

N. meningitidis is a Gram negative β-proteobacterium and a member of the bacterial family Neisseriaceae. It is an aerobic diplococcus and can be either structurally encapsulated or unencapsulated. *N. meningitidis* strains that cause invasive disease are usually encapsulated, which helps with survival of the bacteria during invasive disease and transmission as well as protection from antibodies and phagocytic cells (2). *N. meningitidis* can be acquired through respiratory secretions and attach to human nasopharyngeal mucosa surfaces as a part of normal flora. Carriage can vary between days to several months and is present in 8% to 25% of human populations. Hosted only by humans, transmission of the meningococcus occurs through large respiratory droplets from asymptomatic carriers or patients who are ill with upper respiratory symptoms. Chemoprophylaxis with rifampin, ciprofloxacin, ceftriaxone or sulfonamides is able to eradicate nasopharyngeal carriage of the meningococcus and thus prevent transmission.

Meningococci are classified according to serological typing based on the biochemical composition of the polysaccharide capsule. In total, 13 serogroups have been identified

thus far. However, only six serogroups (A, B, C, W-135, X, and Y) can cause life-threatening disease.

Further characterization of *N. meningitidis* involves the use of multilocus sequence typing (MLST), where 400-500 base pair internal fragments from 7 housekeeping genes considered not to be under selective pressure are sequenced. Meningococcal strains are classified into different sequence types based on polymorphisms in these housekeeping genes (3). MLST is the preferred approach for identifying groups of genetically closely related meningococci as they are grouped into clonal complexes. Most cases of invasive meningococcal disease are caused by a few genetically defined clonal complexes that emerge and spread worldwide. For instance, ST-11 causes most of the serogroup C disease in the United States. In the state of Georgia, the relationship between strain characteristics and the incidence of sporadic meningococcal disease is not well established.

The incidence of meningococcal disease is considered to be cyclical in nature, having peaks and troughs every 5 to 8 years. Disease pattern vary between meningococcal serogroups geographically and over time. In sub-Saharan countries of Africa extending from Senegal in the west to Ethiopia in the east, infamously known as the African meningitis belt, there have been periodic large epidemics of serogroup A meningococcal disease since 1905 with incidence exceeding 1000 cases per 100,000 for some years (4). These patterns have been attributed to climatic changes in the region. Similar to Africa, serogroups A and C have predominated in parts of Asia, where the burden of disease is much less well defined. In other parts of the world including Latin America, Australia, and Europe, serogroups B and C are more dominant and persist endemically over time with lower incidence. Meningococcal serogroups vary by region, but as noted, serogroups A, B, and C account for majority of cases throughout the world (5).

In the United States, the incidence of meningococcal disease in the last quarter century peaked at roughly 1.7 per 100,000 in the mid1990s and then continually declined to approximately 0.35 per 100,000 in 2007 (4). While meningococcal disease occurs year round, the majority of cases occur during the winter and early spring (6). The distribution of serogroups causing disease also has shifted. Serogroup Y increased to almost 50% of cases in the mid-1990s while it only accounted for 2% of all meningococcal infections in the early 1990s (7). In May 2005, the Advisory Committee on Immunization Practices recommended a quadrivalent meningococcal conjugate vaccine, MCV4, for routine use in all U.S. adolescents for serogroups A, C, W-135, and Y protection. The population impact of the vaccine and a second quadrivalent conjugate vaccine has been difficult to determine due to the falling incidence of disease and the initial low vaccine uptake.

While majority of invasive meningococcal cases are sporadic, a total of 69 outbreaks were identified in the United States between mid-1994 and mid-2002, most of which were serogroup C outbreaks occurring in both the community and in organizations such as nursing homes, schools, and colleges (8). This is thought to be due to close contact and crowded living conditions such as in college dorms, where the transmission of the meningococcus is elevated. In addition to the settings described, infants and very young children are at the highest risk of developing meningococcal disease since serum bactericidal antibodies have not yet developed and maternal antibodies have waned. Other individual risk factors for meningococcal disease that have been found are being certain ethnic minorities, smoking, being genetically susceptible (e.g. complement deficiency), having concurrent respiratory infections, and a lower socioeconomic status, which may be a marker for crowding (9).

Surveillance is important for assessing the burden and epidemiology of meningococcal disease. Laboratory based surveillance based on isolation from blood or other normally sterile body site is the gold standard in identifying *N. meningitidis* in cases with clinical invasive meningococcal disease. Non-sterile body sites, such as the pharynx, are not usually cultured since there are many individuals who are asymptomatically colonized with *N. meningitidis*. An ideal surveillance system for invasive meningococcal disease should also be population based in order to capture disease incidence accurately. In addition, active surveillance is preferred since it has increased sensitivity because it elicits reports from healthcare providers and laboratories, which are required to report cases of clinically diagnosed meningococcal disease on a regular basis.

In the United States, the Active Bacterial Core surveillance (ABCs) is an active laboratory and population-based surveillance system that tracks invasive bacterial pathogens. ABCs is a part of the Emerging Infections Program Network coordinated by the Centers for Disease Control and Prevention in collaboration with participating state and local health departments as well as universities. Since December 1988, population based surveillance for invasive meningococcal disease has been conducted prospectively in metropolitan Atlanta as part of an active bacteremia and meningitis surveillance project carried out in conjunction with the Georgia Department of Human Resources and the Centers for Disease Control and Prevention.

Using the surveillance database in metropolitan Atlanta over the past 20 years, we determined the incidence and epidemiologic characteristics of invasive disease due to *N. meningitidis*. In addition, we addressed the geographical and temporal trends in the occurrence of invasive meningococcal disease and the spread of invasive clonal complexes over the years in the community.

Methods

Collection of cases

In the state of Georgia, active population surveillance for *N. meningitidis* has been conducted in the Georgia Health District 3 (Clayton, Cobb, DeKalb, Douglas, Fulton, Gwinnett, Newton, and Rockdale) since December 1988. In January 1997, the surveillance system was expanded to the 20 county Atlanta Metropolitan Statistical Area (Barrow, Bartow, Carroll, Cherokee, Clayton, Cobb, Coweta, DeKalb, Douglas, Fayette, Forsyth, Gwinnett, Henry, Newton, Paulding, Pickens, Rockdale, Spalding, and Walton). Microbiology laboratories servicing acute care hospitals in the surveillance area were enlisted to identify cases of culture confirmed meningococcal disease.

A case of meningococcal disease was defined as the isolation of *N. meningitidis* from a normally sterile site (blood, CSF, pleural fluid, peritoneal fluid, joint/synovial fluid, bone and other internal body sites) from a resident of the defined surveillance area between December 1988 and October 2010. Regular laboratory audits were conducted every six months to evaluate the completeness of active surveillance and to detect additional cases. The use of this surveillance data was approved by the Institutional Review Board of Emory University.

Collection of isolates, serotyping, molecular typing

Isolates were identified by standard methods (e.g., gram-negative diplococci, positive oxidase test, utilization of glucose and maltose). Isolates were also subcultured and additional serogrouping was done at CDC. A viable isolate was subsequently collected and was stored at -70°C in gonococcal broth with 16% glycerol.

To identify clonal groups and closely related strains, MLST was conducted on meningococcal strains that were not previously molecularly typed. The nucleotide sequences of internal fragments of the following genes were obtained: *abc*Z (encoding a putative ABC transporter), *adk* (adenylate kinase), *aro*E (shikimate dehydrogenase), *fum*C (fumarate hydratase), *gdh* (glucose-6-phosphate dehydrogenase), *pdh*C (pyruvate dehydrogenase subunit), and *pgm* (phosphoglucomutase). Gene fragments were amplified from meningococcal chromosomal DNA by using PCR. Sequencing of the amplified fragments was achieved by automated technology performed by Beckman Coulter, Inc. DNASTAR LaserGene8 Seqman was used to assemble the sequences of the 7 genes from each isolate. To identify the sequence type and the defined clonal complex, sequences were then compared with the previously observed allelic sequence in the Neisseria MLST database (http://pubmlst.org/neisseria/).

Statistical Analyses

For each case of invasive meningococcal disease, a standardized case report with basic demographic information was completed. Basic demographic information included age, sex, and race. ArcMap10 was used to geocode US addresses used in mapping the invasive meningococcal cases. Cumulative incidence was calculated using population data from the US Bureau of the Census for 1989 to 2010 for the surveillance areas. Incidence rates are reported as cases per 100,000 population. χ^2 test was used to assess statistical significance. Cases with unknown serogroups have been shown to be genetically serogroups B, C, and Y and thus were imputed by proportionally categorizing into those serogroups (10).

Results

A total of 468 cases of invasive meningococcal disease were detected in the Atlanta surveillance area from 1989 to 2010. As shown in Table 1, 232 of the 468cases (50%) occurred in adults 18 years of age or older. Males accounted for slightly more than 50% of the cases. In addition, among the 468 cases, 255 (55%) occurred in whites and 180 (39%) occurred in blacks.

From 1989 to 2010, the overall average annual incidence was 0.68 per 100,000 population. However, as shown in Figure 1, the incidence of meningococcal disease from 1989 to 1991 was approximately 1.2 per 100,000 and declined to over 0.8 in 1992. The rate of disease then increased and peaked at 1.3 per 100,000 in 1996. Thereafter, the incidence of invasive meningococcal disease declined. Overall, the rate decreased from 1.25 in 1989 to 0.78 in 1999 to just below 0.1 in 2010 (χ^2 for linear trend, $p = 0.007$). The rates of meningococcal disease in the 21st century have been significantly lower overall in comparison to the previous decade.

Serogroup C has accounted for majority of the cases in the first decade of the surveillance. However, the incidence of serogroup C meningococcal disease significantly diminished from 0.81 in 1989 to 0.20 in 1999 to 0.02 in 2009 (χ^2 for linear trend, $p < 0.001$). In comparison, the rates of serogroup B have been more consistent between 1992 and 2001, fluctuating around 0.2 per 100,000, but also have declined since 2001. Also shown in Figure 1, there was the emergence of serogroup Y cases in the mid-1990s. Serogroup Y disease incidence peaked in 1997. Although decreases in serogroup Y incidence were seen after 2001 following the overall decline in incidence, serogroup Y continues to cause disease in the population.

As shown in Figure 2, the highest age-specific incidence of meningococcal disease occurred in infants less than two years of age. In that age group, serogroup B meningococcal disease predominated over the other serogroups (χ^2, $p < 0.001$). While the rates of meningococcal disease were low for other age groups, the data suggest that incidence of serogroup C is significantly higher in young children and adolescents and decreases with age (χ^2 for linear trend, $p = 0.008$). In addition, there is an increase in serogroup Y disease in older adults especially those sixty-five years of age and over (χ^2, $p < 0.001$).

The incidence of meningococcal disease also fluctuated by season. As seen in Figure 3, the peak for cases occurred between January and April, each month accounted for 10% to 12% of all cases between 1989 and 2010. The fewest cases occurred in the months of August, September, and October, each of which accounted for less than 5% of all cases.

Serogroup is a phenotypic marker of isolates. Genetic typing of clonal complex, based on minimum of four MLST gene sequences, was available for 258 invasive meningococcal cases, which accounts for 55% of the total number of cases from 1989 to 2010 in the defined surveillance area. As shown in Table 1, over 85% of the isolates for which the MLST was available belonged to one of the five clonal complexes: ST-11/ET-37, ST-23/A3, ST-32/ET-5, ST-41/44, and ST-162. Seven sequences of isolates had new STs that were not present in the MLST database.

As shown in Table 2, among the 108 isolates of serogroup C meningococcal disease, almost all of them (94%) are caused by the ST-11 complex. Similarly, nearly all of the 68 serogroup Y isolates (93%) were characterized as members of the ST-23 complex. In contrast, the 70 isolates of serogroup B meningococcal disease were distributed into various clonal complexes. ST-41/44 caused almost 50% of serogroup B cases, while ST-

32 and St-162 as well as other clonal complexes were responsible for the other serogroup B cases.

Figure 4 illustrates the distribution of invasive meningococcal cases in the defined surveillance area including the Health District 3 (HD3) and the expansion into the Metropolitan Statistical Area (MSA) from 1989 to 2010. Figure 5 illustrates the distribution of various serogroups of cases categorized into 4 year time periods. In the first two panels (1989-1992 and 1993-1997), surveillance was restricted to the HD3 area. During those time intervals, Fulton and Cobb Counties averaged over 1.5 cases per 100,000 on an annual basis, In addition, over half of the reported cases occurred in these two counties.

In Figure 5, the ArcMap10 maps demonstrate that cases decreased over time and became more distributed in the surveillance area. For example, there was an emergence of serogroup Y cases between 1993 and 1997, which clustered in Fulton County. The next panel illustrates a similar scenario, but cases were also noted in Clayton County and DeKalb County. After 2001, the decline in cases also eliminated the clustering effect, seen in the first decade of the surveillance.

The temporal trend of *N. meningitidis* clonal complexes is shown in Table 3 and reflects the distribution of the associated serogroups over time as depicted in Figure 5. Seen in Table 3, ST-11 complex, mostly serogroup C, caused the majority of the cases from 1989 to 1996 until the emergence and sharp increase of the ST-23 complex in the late 1990s. Between 1997 and 2000, ST-23 complex caused 40% of the cases whereas ST-11 complex was responsible for roughly 33% of the isolates. The distribution of ST-41/44 and other clonal complexes was distributed geographically and throughout each time interval with no particular trends noted. However, serogroup B and associated clonal complexes was persistent over the years in causing invasive meningococcal disease in the population.

Discussion

The changing incidence observed in the Atlanta surveillance area is consistent with national trends. In the United States, several studies found that the rates of invasive meningococcal disease between 1989 and 1991, ranged from 1.3 per 100,000 to 0.9 per 100,000 (7). Between 1992 and 1996, the incidence of meningococcal disease increased from 0.8 to 1.0 per 100,000 (6). Subsequently, the annual incidence of disease has decreased 64% from 0.92 in 1998 to 0.33 per 100,000 in 2007 (11). However, the reasons behind the dramatic decrease in the incidence of meningococcal disease after 2001 are not well understood. Changes in environmental factors as well as crowding and population immunity to circulating strains may have contributed to decreased transmission or the risk of invasive disease (4). The decline in the incidence of invasive occurred prior to the introduction of MCV4 and consistent with previous findings, the effects of the vaccine have not been clearly observed (11).

During the 21-year active population based surveillance, infants and young children under the age of two years had the highest risk of developing invasive meningococcal disease. This increased risk is most likely due to a lack of serum bactericidal antibodies in this population and waning of maternal antibodies that would have otherwise protect from invasive disease (12). Younger children and adolescents had a higher incidence of serogroup C disease, which might be attributed to risk factors and social determinants such as close contact, crowding or contact in schools and special living conditions such as college dorms. This is reflected in increased transmission of meningococci in the older children and adolescents where the carriage rates for *N. meningitidis* are the highest (13). For older individuals, especially those 65 and over, serogroup Y had a high incidence of disease. The reasons for this increased risk for serogroup Y are unclear.

However, previous findings have found that serogroup Y meningococcus causes respiratory infections such as pneumonia in adult populations (14). It is important to monitor age-specific incidence as the distribution will consequently affect the recommendations for the MCV4 or future serogroup B vaccines.

Serogroup C consistently accounted for a higher proportion of invasive meningococcal disease in the Atlanta surveillance area until late 1990s. Molecular characterization showed that clonal complex ST-11 has caused the majority of the invasive disease. This demonstrates that most of the serogroup C invasive cases occurring in the metropolitan Atlanta area over the past twenty years were caused by closely related strains, which slowly circulated in the community and caused majority of the endemic serogroup C disease. These findings were consistent with a study conducted in Atlanta examining the relatedness of serogroup C strains between 1988 and 1994, using multilocus enzyme electrophoresis and pulse-field gel electrophoresis (15). Our current study found that there have been no significant changes in the molecular epidemiology of serogroup C meningococcal disease for the last decade and the ST-11 strains are still circulating in the community and causing sporadic disease.

Serogroup Y emerged in the early 1990s and increased in incidence through the mid-late 1990s. This is shown in the maps as a cluster inner city Fulton County between 1993 and 1996 but dispersed into the larger MSA with time. The temporal trend of serogroup Y incidence is consistent with national trends reporting increasing incidence in the mid-1990s (16). We found that increasing Y disease in metropolitan Atlanta was attributed to the appearance and the spread of clonal complex ST-23. The majority of all serogroup Y cases occurring in metropolitan Atlanta were caused by the ST-23 clonal complex. This can be explained by the introduction of a new distinct clone into the community and/or waning population immunity to serogroup Y. In 1998, a carriage study examining

nasopharyngeal specimens from 1816 high school students from hypersporadic counties in the Atlanta region found rate of carriage to be 7.7% and of these, 48% were serogroup Y. In addition, roughly 40% of the carriage isolates were characterized as serogroup Y ST-23/ET-508 strains (17). This is consistent with our findings and suggests that the high rates of serogroup Y carriage and acquisition of the ST-23/ET-508 clone may have resulted in the increased incidence of serogroup Y meningococcal disease observed in the late 1990s. From 2006 to 2007, a separate carriage study reported a much lower proportion of serogroup Y carriage. However, more than half of the serogroup Y carriers were found to carry the same sequence type at each of the three time points (baseline, 6 weeks, and 8 months) suggesting a prolonged ST-23 clonal complex carrier state (18). The lower frequency of serogroup Y and overall meningococcal carriage is reflected in the decrease in invasive meningococcal cases between 2006 and 2007 found in our study. Molecular typing of additional and future isolates are needed in order to characterize the emergence of serogroup Y as well as aid in vaccine and other prevention efforts to eliminate serogroup Y meningococcal disease in Atlanta.

In contrast to serogroups C and Y, we found that serogroup B meningococcal isolates in metropolitan Atlanta over the past twenty years were from several distinct genetic lineages. This is consistent with the global distribution of clonal complexes for serogroup B where clonal complexes ST-41/44 and ST-32 cause a little over half of the invasive cases in the world while other complexes compromise the other serogroup B cases. This suggests that there is greater genetic diversity and thus antigenic diversity in serogroup B strains that cause sporadic serogroup B disease. Studies have also found that other related and novel strains are occurring worldwide and the diversity of clonal complexes causing serogroup B presents a challenge to eradicate (19). Hypervirulent serogroup B strains are especially of concern due to the absence of a vaccine for serogroup B prevention, since serogroup B capsule is poorly immunogenic and is not included in

MCV4. Studying the distribution patterns of clonal complexes may provide better insights for creating an effective vaccine for serogroup B meningococcal disease.

This study is one of the first to characterize *N. meningitidis* strains from over two decades in order to better define invasive meningococcal disease. However, only 55% of all isolates have to date been characterized successfully for genetic type and this may bias the distribution of clonal complexes observed. Molecular typing presented a unique challenge because the extent of recombination in meningococci is high compared to some other bacterial populations. Additional strains can be characterized in order to provide a more complete set of molecular and genetic data for the invasive isolates in the surveillance system.

ABCs is an active population surveillance system that identifies almost all cases in a defined population. This avoids selection bias associated with hospital based case series or passive reporting systems. However, ABCs may underestimate the burden of meningococcal disease in the United States since only cases where *N. meningitidis* is isolated from a normally sterile body sites are captured. Although the incidence of meningococcal disease has dramatically decreased over the past decade, continued surveillance is essential in understanding and predicting the not well understood dynamic changes in the epidemiology of meningococcal disease. In addition, molecular characterization of meningococcal isolates is important in determining the spread of specific clonal complexes in the community.

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Tables

Table 1 Demographic Characteristics of Cases of Meningococcal Disease in Atlanta, 1989-2010

Characteristics	Number of Cases (%)
Age group, years	
<2	103 (22.0)
2-4	39 (8.3)
5-17	94 (20.1)
18-39	118 (25.2)
40-64	69 (14.7)
65+	45 (9.6)
Sex	
Male	257 (54.9)
Female	211 (45.1)
Race	
White	255 (54.5)
Black	180 (38.5)
Other*	33 (7.1)

*Include American Indian, Asian/Pacific Islander, Other and Unknown

Table 2 Meningococcal Clonal Complexes by Serogroup in Atlanta, 1989-2010

Clonal Complex	B (n=70)	C (n=108)	Y (n=68)	Other* (n=12)
ST-11	3	102	0	1
ST-23	0	0	63	4
ST-32	14	0	0	0
ST-41/44	26	0	0	0
ST-162	8	0	0	1
Other	15	5	4	5
Not Assigned	4	1	1	1

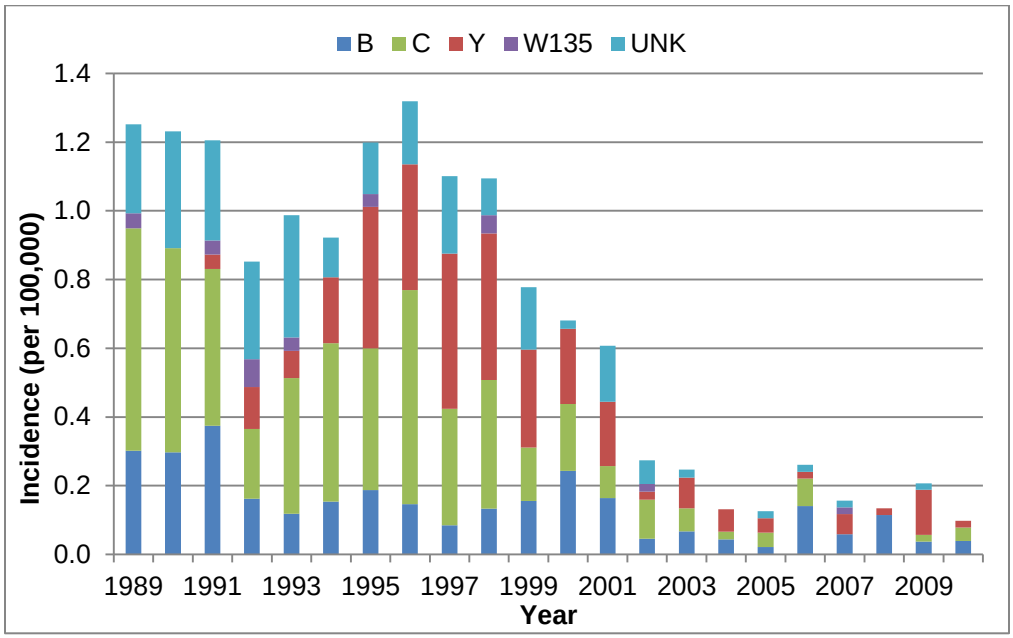
*Includes W135, Z, and non-groupable serogroups.

Table 3 Meningococcal Clonal Complex by Years

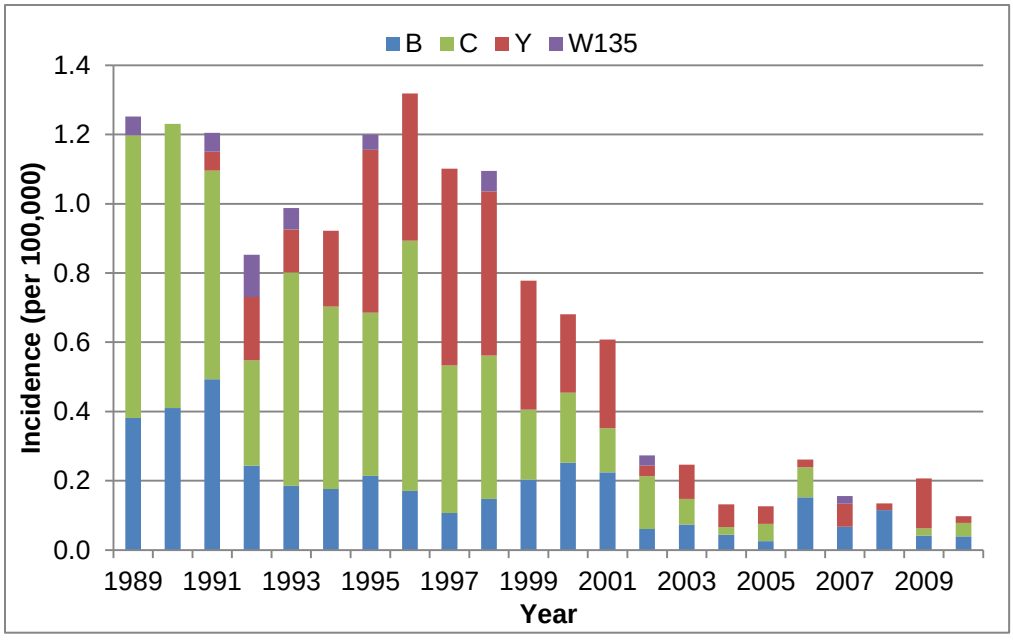
Clonal Complex	1989-1992 (n=37)	1993-1996 (n=51)	1997-2000 (n=85)	2001-2004 (n=45)	2005-2008 (n=31)	2009-2010 (n=9)
ST-11	24	37	28	11	4	2
ST-23	0	7	32	15	8	5
ST-32	1	0	2	5	5	1
ST-41/44	6	1	11	4	4	0
ST-162	0	3	4	1	1	0
Other	6	2	5	8	8	0
Not Assigned	0	1	3	1	1	1

Figures

Figure 1 Incidence of Meningococcal Disease by Serogroups, 1988-2010 **(A)**. Same figure with Unknown serogroups imputed into serogroups B, C, Y, and W135 **(B)**.

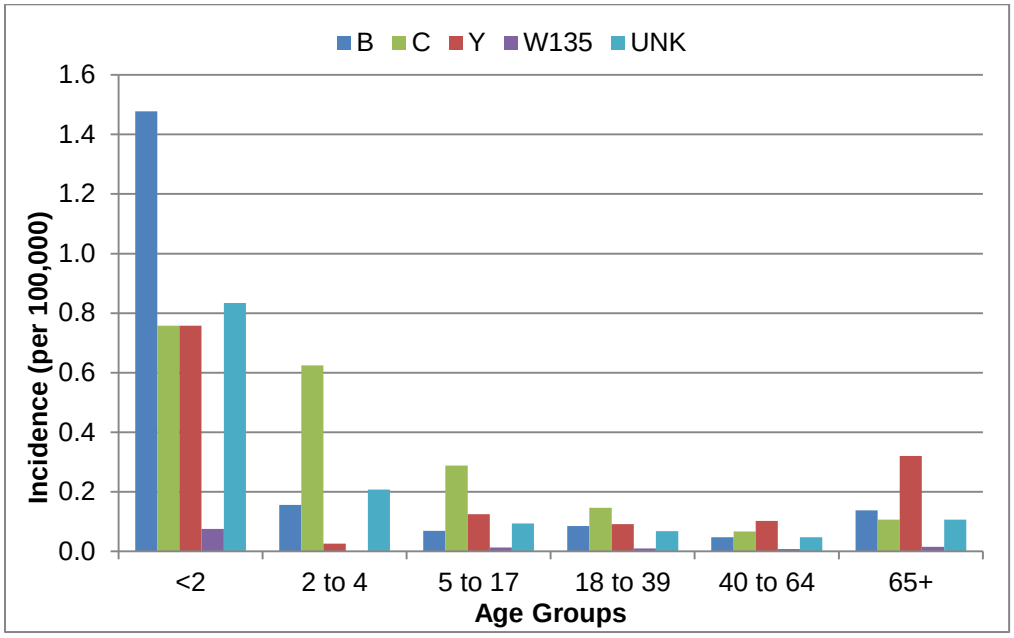


A

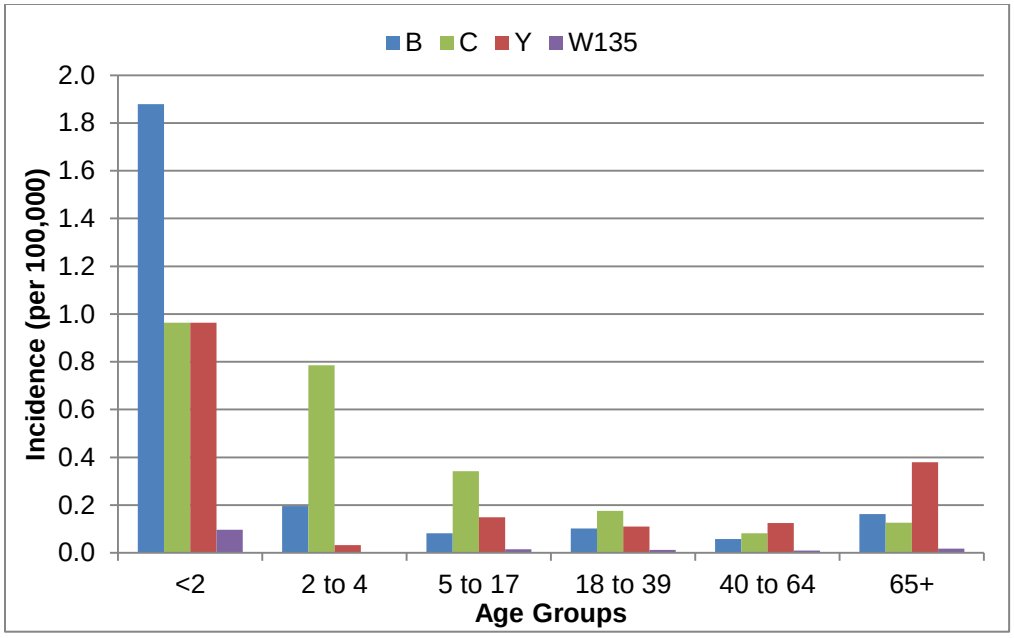


B

Figure 2 Cumulative Incidence of Meningococcal Disease by Age Group and Serogroup **(A)**. Same figure with unknown serogroups imputed into serogroups B, C, Y, and W135 **(B)**.



A



B

Figure 3 Seasonal Variations in Cases of Meningococcal Disease, 1988-2010.

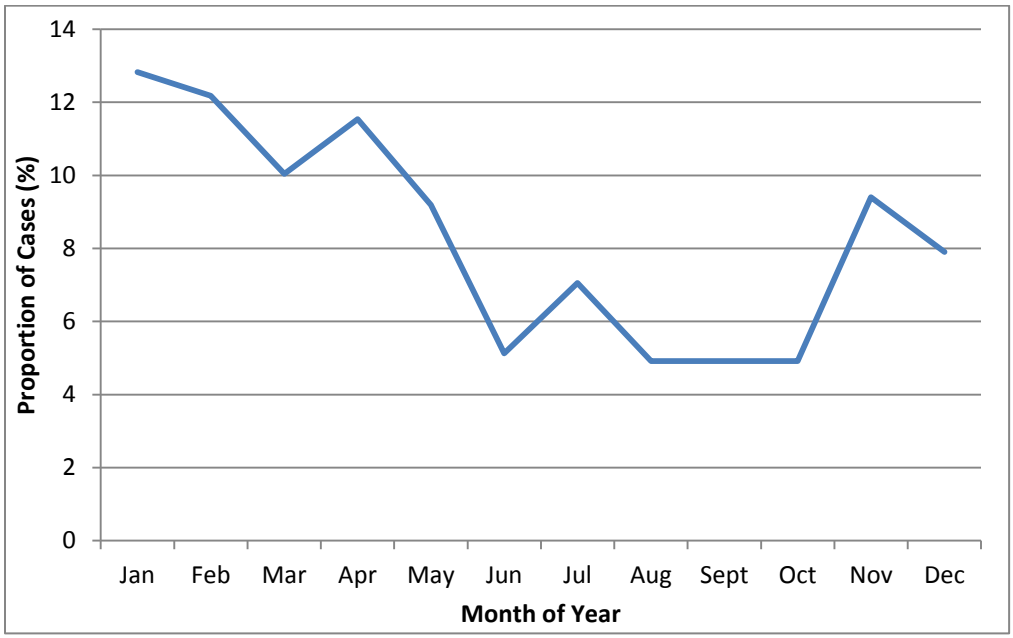


Figure 4 All Reported Cases in Metropolitan Atlanta, 1989-2010. Yellow shading represents the HD3 surveillance area while light green shading represents the additional MSA surveillance area.

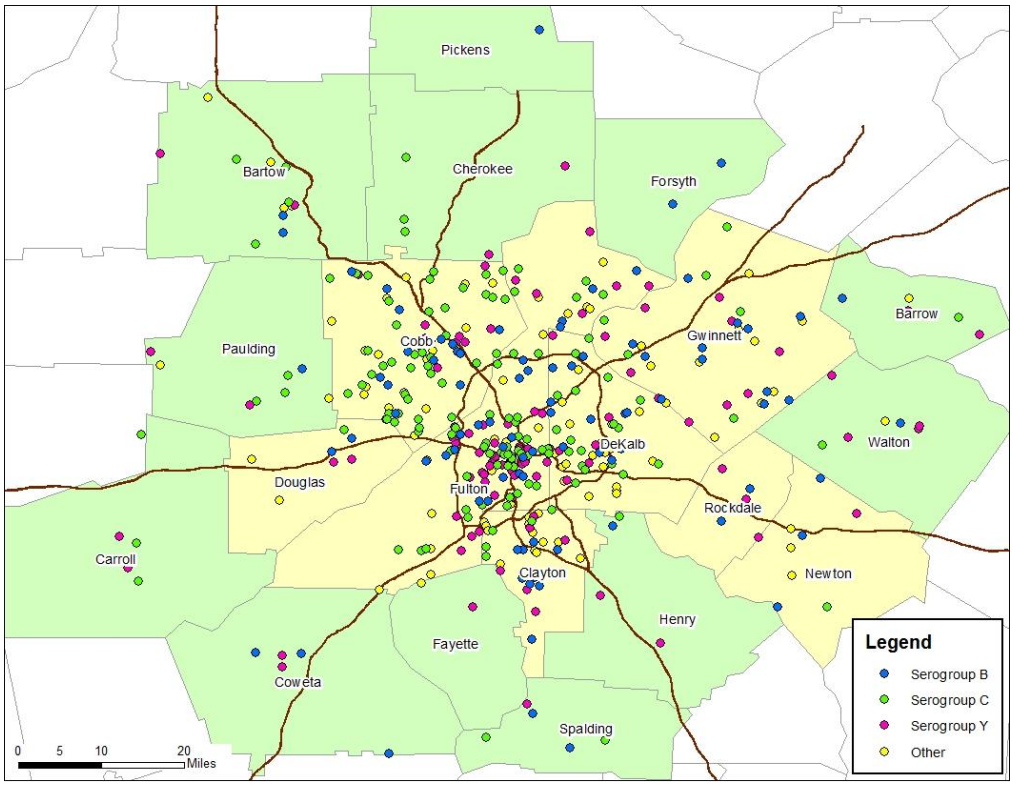
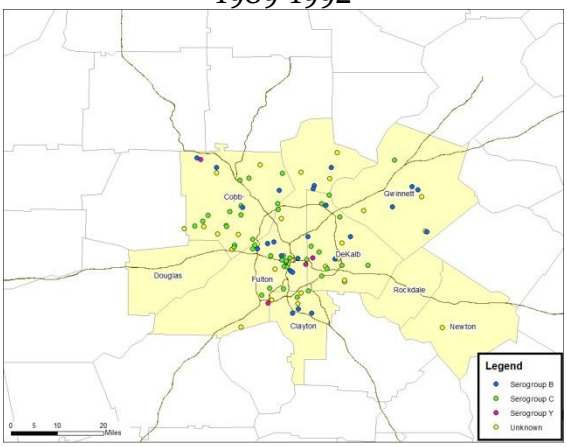
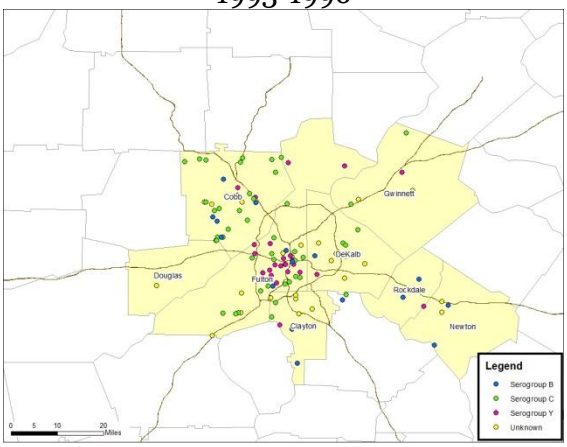


Figure 5 All Reported Cases in Defined Surveillance Area by Years. Yellow shading represents the HD3 surveillance area while light green shading represents the additional MSA surveillance area.

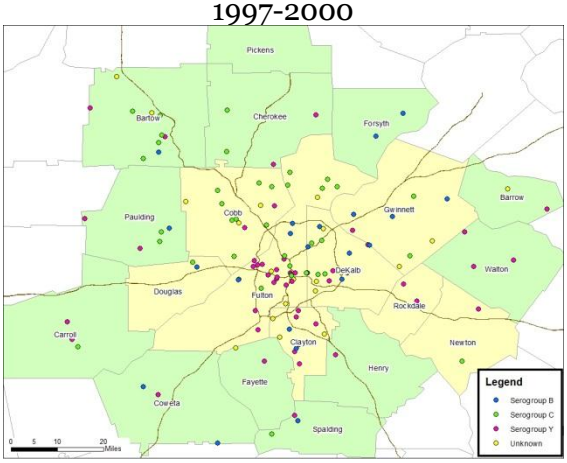
1989-1992



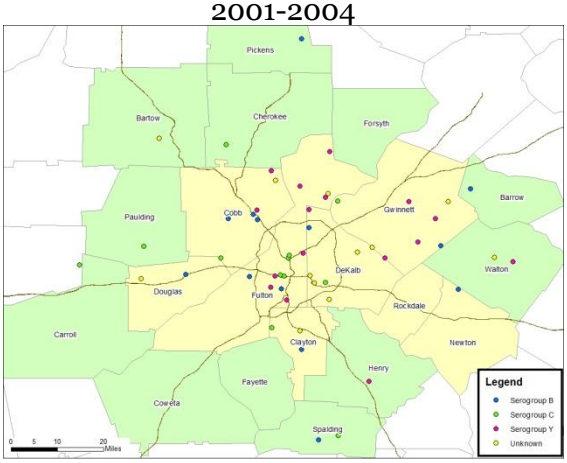
1993-1996



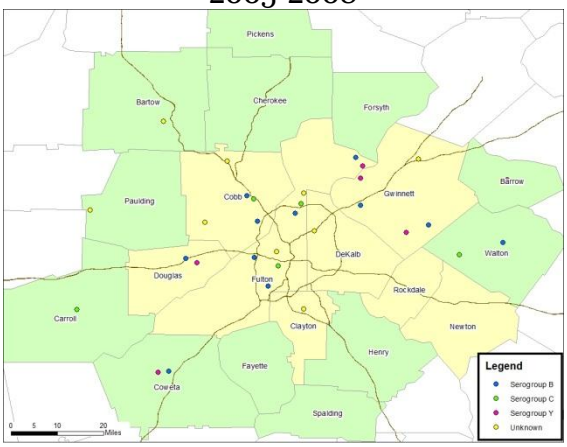
1997-2000



2001-2004



2005-2008



2009-2010