

Meningococcal Disease

Becka CM^{1*} and Chacón-Cruz E²

¹Department of Medicine, Xochicalco University, School of Medicine, Tijuana, Baja California, Mexico

²Department of Medicine, Tijuana General Hospital, Baja California, Mexico

*Corresponding author: Chandra M Becka, Xochicalco University, School of Medicine, Tijuana, Baja California, Mexico, Tel: 1-208-546-2500; E-mail: cmbecka@gmail.com

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Abstract

Meningococcal disease is one of the great bacterial threats to human health. Even in the age of antibiotics and vaccines, it remains one of the primary causes of bacterial meningitis worldwide. The causative agent, *Neisseria meningitidis*, is a gram negative, fastidious diplococci that commensally inhabits the human nasopharynx. Transmission occurs through close contact with aerosol and respiratory secretions of infected carriers. The disease occurs both sporadically and in epidemics. Endemic areas with high carriage rates have also been identified. The purpose of this review is to examine the current status of the disease and identify the obstacles that the scientific community will encounter in the face of technological advances, changing environment and disease evolution.

Keywords: Meningococcal disease; *Neisseria meningitidis*

Introduction

Meningococcal disease (MD) was first documented in 1805 by Swiss physician Gaspard Vieusseux who described a “*fièvre cérébrale maligne non contagieuse*” (non-contagious malignant cerebral fever) [1]. The first reported cases in the western hemisphere appeared one year later [2,3]. It was believed to be non-contagious. The transmissible nature was not understood until the late 19th century. It was not until 1887 that *Neisseria meningitidis* (*Diplococcus intracellularis meningitidis*) was cultured and identified as the causative agent [3,4]. A system for classifying the different meningococcal isolates into serogroups I-IV was developed in 1915 [5]. It was later modified to the system currently used, which is based on structural differences in the polysaccharide capsule [6].

Up to the 1900's there was no effective treatment for MD. Simon Flexner was the first to synthesize an antiserum, derived from injecting live bacteria into horses, that was able to diminish mortality in some outbreaks [7]. With the arrival of Sulfanamides in the 1930's, mortality rates were greatly reduced [8,9]. Increasing resistance to sulfonamides, however, prompted effective vaccine development in the 1970s [10,11].

Serogroups

Currently, there are 12 serogroups of *N. meningitidis* that have been identified. Serogroups A, B, C, W-135, Y and X represent the most common causes of invasive meningococcal disease. *N. meningitidis* is found with and without a capsule; however, pathogenic strains are always encapsulated [6]. The polysaccharide capsule is an important defense mechanism for evading the body's antibody and complement-mediated defenses and inhibiting phagocytosis [12]. The capsule of most pathogenic strains (serogroups B, C, W-135, X, and Y) is composed of sialic acid derivatives [13]. Only serogroup A has a nonsialic acid composition, based on N-acetyl-mannosamine-1-phosphate. The serogroup B capsule contains $\alpha(2-8)$ -linked N-acetylneuraminic acid, the same polymer that is a component of the

human neural cell adhesion molecule (NCAM), which impedes the development of a successful polysaccharide vaccine [14]. *N. meningitidis* has capsular switching abilities that play an important role in defense and epidemiology. Capsular switching has been seen in sialic acid strains and is another important defense mechanism of the meningococci [15]. The capsule has also been the target for vaccine development.

Epidemiology

In the twentieth century *N. meningitidis* joined *Haemophilus influenzae* and *Streptococcus pneumoniae* as one of the leading causes of bacterial meningitis and septicemia. Despite being a relatively new pathogen in human history, *N. meningitidis* has proven to be a formidable adversary; initially resulting in mortality rates of up to 80% [7]. During World War I and II, serogroup A was prevalent throughout the world, causing large epidemics that were responsible for thousands of deaths. Subsequent to World War II, epidemiology shifted from serogroup A to serogroups B and C in industrialized countries. The introduction of vaccines and chemoprophylaxis significantly decreased the disease burden in industrialized countries [16].

Carriage rates differ among age groups with infants exhibiting a lower rate of 4.5% and individuals greater than 50 years old evidencing carriage rates at almost 8%. The highest carriage rates are seen in late teen years and early adulthood, with nearly 10% in the general population [17].

Meningococcal disease rates are highest among infants and elderly, with a peak in incidence in young adults. Endemic MD more frequently affects infants and young children, whereas outbreaks occur at a higher rate in adolescents and young adults [6]. Age-related distribution is also seen in the etiological agent. Infants have a higher incidence of infection from serogroup B. Serogroup C affects adolescents and young adults and the elderly see and increased incidence of serogroups B and Y [6].

Meningococcal disease presents with unique seasonal variations throughout the world. In sub-Saharan Africa, highest disease rates

occur during the dry season. In North America, however, disease rates spike in winter and spring [18].

Serogroups B and C are responsible for the majority of cases in Europe and the Americas. However, serogroup A is more prevalent in Africa and Asia. More recently, serogroup X has become prevalent in Africa's meningitis belt [19].

Middle East and Africa

The Middle East and Africa is plagued with endemic areas of MD, specifically a sub-Saharan region known as the meningitis belt [20]. Rates of MD in this region can exceed 1000 cases per 100,000. Serogroup A is still the most prevalent cause in the meningitis belt. However, extensive vaccination efforts since 2010 have had success in significantly diminishing the incidence of serogroup A MD. Serogroups W-135, C and more recently X, have also caused epidemics in the region. Several factors affect the frequency of outbreaks in the region. Social conflict, economic conditions, public health obstacles, and customs of the region all affect the incidence of MD. There have also been several outbreaks associated with the annual pilgrimages that pass through the region. The Hajj and Umra pilgrimages bring overcrowded masses with poor public health practices [21].

Asia

Epidemiological data is only available from a limited number of Asian countries, with most having little or no data available. Japan, Hong Kong, Korea, the Philippines, Singapore, Thailand and Taiwan are the only Asian countries with surveillance systems for meningococcal disease, all of which are passive reporting systems. Throughout China, Bangladesh and India, serogroup A has been reported as the major cause during years of large epidemics. Throughout Asia, serogroup B is most commonly responsible for sporadic and endemic cases [22]. Reports of endemic serogroup B and C outbreaks have been reported throughout Japan, China and Taiwan [3].

Europe

Europe, like other industrialized regions is most afflicted by serogroups B and C. In most European countries there is adequate surveillance, which has contributed to good understanding and vaccine coverage in the region. The widespread use of the MenC vaccine has caused a decline in serogroup C outbreaks. Serogroup B will continue to be a dominant cause until more universal vaccine coverage can be implemented. More recently, incidence of serogroup Y has been increasing, and it is now the third most common cause of MD in Europe [23]. Sweden has a higher proportion of serogroups W-135 and Y. In Eastern Europe and Russia, serogroup A still persists [16].

Americas

In the United States MD rates have been steadily declining in the last decade. The current incidence rate is 0.14/100,000 per 100,000 population [24]. The majority of the cases occur sporadically and cause is almost equally distributed between serogroups B, C and Y. Serogroup B is responsible for nearly 60% of cases occurring in infants up until 59 months of age. In individuals older than 11 years of age, serogroups C, Y and W cause the majority of cases [24].

In Canada, serogroup B is responsible for 50-80% of MD. Incidence of serogroup C in Canada has, with the exception of a few outbreaks between 1999 and 2001, steadily declined. Rates of serogroup Y are low and have remained relatively stable [25]. Both the United States and Canada have active surveillance systems in place throughout the countries and have implemented vaccination guidelines accordingly [26].

Historically, Mexico has reported a low incidence of MD, citing as low as 2 cases per year [27]. Larger epidemics were reported in the 1940s, but up until the mid-2000s, subsequent information has been either inconsistent or non-existent. Recently, several reports of endemic areas of MD in Northern Mexico have surfaced, changing the perspectives. In Mexico, there was no country-wide active surveillance system in place until recently. A three year active surveillance system composed of 10 hospitals throughout Mexico reported significantly higher rates and revealed that MD is the leading cause of bacterial meningitis in the country [28,29]. Highly endemic areas of disease have been seen along the United States-Mexico border region, with rates that surpass national averages in both countries [30]. Currently, the majority of cases is caused by serogroup C, followed by B and Y [31,32].

Surveillance is not available in all countries of South America, but those with reliable systems have reported similar epidemiological trends to those of Europe and North America. During the early-mid 1900's serogroup A predominated, but there was a shift to serogroup B and C by the 1970s. Brazilian epidemics in the 1970s were the first successful experiences with polysaccharide vaccines for serogroups A and C [33]. Subsequently, serogroup B became the most common cause. Despite the availability of effective vaccines, serogroup C has risen once again to be the most common cause of MD in Brazil. Argentina has seen similar epidemics due to serogroups B and C. Currently, serogroup B is responsible for the majority of cases in Argentina, Chile, and Uruguay. Serogroup Y has been reported as the main cause of MD in Colombia and Venezuela in the last 2 decades, surpassing serogroup B [34]. Argentina, Chile, Brasil and Uruguay have seen all seen an increase in cases caused by serogroup W135 since 2011 [35,36]. Hypervirulent strains have been linked to a clonal complex that originated in 2000 during the Hajj pilgrimage and has since dispersed [35].

Risk Factors

Environmental and socioeconomic factors predisposing to infection have been described in several studies. Notably, low socioeconomic status, crowded living conditions, urban residence and exposure to tobacco smoke all enhance susceptibility to meningococcal infection [37-40]. There have been consistently higher incidence rates among new military recruits and college freshmen. However, overall incidence rates among other military personnel and college students do not differ from that of the general population [41-43]. Concurrent viral infection also predisposes to disease acquisition [44,45].

Clinical Presentation

Development of disease is dependent on contact with a virulent strain of meningococci and independent risks affecting host susceptibility [46]. There are several factors that predispose to MD. Deficiencies of complement-mediated immunity, specifically C5-C9, give the most susceptibility. Humoral immunity also plays an important role in defense and greatly influences age-related incidence.

Absence of splenic function also predisposes to MD [37]. Severity of the disease is directly related to the amount of circulating bacteria and endotoxin released [47-49].

Invasive meningococcal infection is responsible for a wide clinical spectrum. Manifestations occur within 1-14 days of infection [46]. Initial signs and symptoms mimic those of other bacterial infections, making prompt identification difficult. Meningitis occurs in 50-70% of cases [50]. Fever, sudden onset of headache, photophobia, neck stiffness, nausea, vomiting and altered mental status are all characteristic symptoms [37,47]. Less frequent presentations are pneumonia, conjunctivitis, otitis media, epiglottitis, urethritis, pericarditis, arthritis. Meningococcal pneumonia presents more frequently in the elderly and immunocompromised hosts.

The most severe manifestation is septicemia, or meningococemia, which characteristically presents with abrupt onset of fever and a purpuric rash. Patients can develop fulminant meningococcal sepsis (FMS) within hours and may not present signs of meningitis. This presentation occurs in 5-20% of cases. The disease can rapidly progress to septic shock, acute adrenal hemorrhage (known as Waterhouse-Friderichsen syndrome) and ultimately multiorgan failure [37].

The overall mortality of MD is between 10 and 15%, even with aggressive treatment [6]. Sequelae of IMD can be as devastating as the disease itself and occur in 11-19% of survivors [51]. Immune complex-mediated arthritis and pericarditis can occur 4-7 days after the disease. Neurological impairment, hearing loss, seizures, visual loss, motor deficits, behavioral difficulties, chronic pain, skin scarring and amputations are among the sequelae that have been reported [46,52]. A small number of people can develop chronic MD, characterized by episodes of fever, arthralgias, arthritis and recurrent rash.

Diagnosis, Treatment and Prophylaxis

Meningococcal disease progresses rapidly, presenting in a matter of hours. Prompt diagnosis and initiation of antibiotic treatment is essential. Definite diagnosis requires identification of the causative agent *N. meningitidis* in body fluid. Prior to the administration of antibiotics, it is necessary to obtain blood and CSF cultures as sensitivity diminishes quickly thereafter. Polymerase chain reaction (PCR) in blood or CSF is highly specific (nearly 100% for both) but is also time-sensitive. It can be used 96 hours within treatment with antibiotics [53].

Antibiotic therapy should be initiated without delay if MD is expected. *Neisseria meningitidis* has a high sensitivity to many antibiotics. Penicillin and chloramphenicol have been used since the 1950s, after high resistance to sulfonamides appeared. Currently, cephalosporins are routinely the drug of choice, due to penicillin-resistance strains. Rifampin is recommended for all close contacts. Alternatively, ciprofloxacin, ofloxacin, minocycline, and ceftriaxone can be administered [47].

Vaccination

The need for vaccination became apparent in the 1960s, when it was realized that the excessive use of antibiotics caused mass resistance. Currently there are three types of vaccines that are available for use: polysaccharide, conjugate and a multicomponent protein-based vaccine that covers serogroup B (Table 1).

Component	Vaccine	Coverage	Advantages/Disadvantages
Polysaccharide	Mengivac® Sanofi Pasteur	A and C	Effective for control of outbreaks Limited use in infants in young children Poor T-cell response Poor booster response
	Menomune® Sanofi Pasteur	A, C, W135 and Y	
	AC Vax® GlaxoSmithKline	A and C	
	ACWY Vax® GlaxoSmithKline	A, C, W135 and Y	
Glycoconjugate	Meningitec® (MenC-CRM) Pfizer	C conjugated to CRM197	Enhanced T-cell response, prolonged immunogenicity Safe for use children >2 years of age Long duration of protection Good response to booster
	NeirVac® (MenC-TT) Baxter Bioscience	C conjugated to tetanus toxoid	
	Menjugate® (MenC-CRM) Novartis	C Conjugated to CRM197	
	MenAfriVac® (Serum Institute of India Ltd.)	A	
	Menovo® (MCV4-) Novartis	A, C, W135 and Y	
	Menactra® (MCV4-DT)	A, C, W135 and Y	

	Sanofi Pasteur	conjugated to diphtheria toxoid	
	Menitorix® (MenC-Hib-TT) GlaxoSmithKline	A, C, W135 and Y + Hib conjugated to tetanus toxoid	
Protein-based	Trumenba® (Bivalent rLP2086) Pfizer	B	Safe for use children > 2 years of age
	Bexsero® (4CMenB) Novartis	B	

Source: Adapted from published data [51,54,57].

Table 1: Current meningococcal vaccines.

Polysaccharide vaccines were the first to be developed and although they provided the first protection, they had many inadequacies. Polysaccharide vaccines are poorly immunogenic in children younger than 2 years, a primary risk group. They are available in bivalent, trivalent and tetravalent. In industrialized nations, tetravalent vaccination (groups A, C, Y and W-135) is employed to ensure maximal coverage of recommended groups. They have largely been replaced by conjugate vaccines, for the greater benefits. However, polysaccharide vaccines may still have utility in controlling outbreaks [55].

Conjugate vaccines against group C, group A, and tetravalent (A, C, Y and W-135) have proven to be more effective for routine vaccination. Unlike polysaccharide vaccines, conjugate vaccines confer a strong T-cell response, immune memory and a longer duration of coverage. There is also evidence of reduction of carriage and herd immunity that is not found with polysaccharide vaccines [56]. Conjugate vaccines have been widely used since 2005 in Canada, the United States and Europe [55].

The difficulties in developing an effective vaccine against serogroup B stem from the poor immunogenicity of the capsule and a high heterogeneity in the genetic and antigenic makeup of group B, an effective vaccine against the capsule of serogroup B was not feasible. The 4CMenB vaccine was developed using reverse vaccinology, identifying the ideal antigens from the group B genome. Four antigens, to include Neisserial adhesion protein (NadA), Neisseria heparin binding antigen, factor H binding protein, and outer membrane vesicle, comprise a vaccine capable of covering all strains of group B [14,57].

With the arrival of a successful vaccine against serogroup B, public health systems worldwide are reevaluating the recommendations to include coverage of serogroup B. The 4CMenB vaccine (Bexsero) developed by Novartis has been tolerated well by infants and young children, as well as adults and elderly individuals. Currently, the European Union, Canada, Australia, and Chile have all licensed 4CMenB vaccine in ages 2 and up [57]. The United States recently approved use of meningococcal B vaccines for the control of outbreaks individuals 10-25 years of age in 2015 [58].

In the United States, routine vaccination is recommended of infants greater than 2 months that are at an increased risk, adolescents 11-18 years, and of persons of high risk [51]. Most European countries and Canada have similar recommendations. Vaccines against serogroup B have only recently been developed.

Although serogroup A is not a prevalent cause in Europe and the Americas, it has been a substantial burden in Africa and Asia for the past century. In 2010, African nations began conducting massive campaigns with a new meningococcal A conjugate vaccine. Thus far, 217 million people have been vaccinated in 15 different countries of the African meningitis belt [59].

South America has also implemented vaccination programs targeting specific serogroups. Brazil has successfully introduced vaccination campaigns to reduce the rate of MD for serogroup C, which caused the majority of the cases in that country during the last decade [60,61]. Chile has implemented routine vaccination with tetravalent conjugate vaccine of children ages 9 months to 5 years due to outbreaks of serogroup W [62].

Overcoming challenges

Surveillance

Active surveillance is the cornerstone in understanding epidemiological trends and implementing appropriate preventions. However, much of the world has yet to recognize the need for surveillance. Underreporting, absence of established surveillance systems, insufficient diagnostic methods, inconsistent case definitions and social afflictions all affect the overall understanding of MD [35].

While there are several countries of Asia have implemented systems of surveillance, none have implemented active surveillance systems [22]. Although reports of MD in India exist, researchers have stated that there is not reliable data upon which conclusions of epidemiology can be made due to inadequate surveillance systems [63].

Countries in Latin America have also faced obstacles in implementing reliable surveillance systems and several countries have yet to establish an active system. Deficiencies in data have led to the false implication that MD is not a great burden and therefore does not require further action. This has been disproven by smaller studies that have reported substantially higher incidence of disease than national data [29-32].

Evolving disease

The epidemiology of MD is in constant evolution. Despite advances in prevention, diagnosis and treatment in the past century, MD remains a major threat to public health worldwide. With the implementation of vaccination programs, the etiology has shifted and

new serogroups have emerged as important causes of MD. Currently serogroups B and C are responsible for the majority of cases of MD worldwide. The impact that more effective and widely available vaccines will have on overall epidemiology has yet to be seen. Historical trends indicate that with the control of one serogroup, another will emerge. This phenomenon is already being seen in Africa with serogroup X and while it cannot yet be determined that vaccination is a direct cause of class switching, the necessity for developing effective vaccines against serogroup X has already been identified [19].

Resistance

Antibacterial resistance to community-acquired pathogens is a great threat to global health. Prior to antibiotics, the mortality rate of MD could exceed 80%. Cases of quinolone-resistant *N. meningitidis* have already been reported throughout the world [64-66].

Climate change

Meningococcal disease is greatly affected by environmental factors. Several connections have been made between outbreaks of disease and changes in climate worldwide. In Africa, the onset of meningitis disease has been marked by the arrival of windy, dry and dusty conditions [67,68]. This has also been suggested in northern Mexico, though no study has specifically investigated this matter [31]. Methods of predicting incidence of MD based on current climate have been proposed, but have not yet been accepted. Recognizing the effect that the climate change has on infectious disease is important in maintaining control. It has been suggested that understanding climate change could prove useful in predicting epidemiological climate change.

Conclusion

A rapidly evolving landscape of technology has brought spectacular new developments to the medical world. In the past 100 years we have made significant advances in understanding and managing disease. Despite advances, the management of MD remains a challenge.

Developing consistent universal active surveillance systems is essential in completely understanding the disease burden worldwide. Emphasis should be placed on understanding the environmental influences on MD, especially given the changing climate. Ignoring climate change, could pose a great threat to the future management of infectious disease if the effects are not completely understood.

Novel technologies in vaccinology have led to the development of effective vaccines for serogroup B, a previously unobtainable feat. Aggressive vaccination campaigns across the world have alleviated the burden of disease. However, many countries still fail to recognize the importance of MD and have yet to include coverage against *N. meningitidis* in routine immunization schedules. Developing universal standards for prevention is the next step in managing MD in the future.

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