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Global Epidemiology and Prevention of *Neisseria Meningitidis*

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Abstract: **Meningitis is an acute infection that causes inflammation of meninges, the protective membrane covering the brain and spinal cord. Meningitis can be bacterial, viral fungal, or noninfectious meningitis depending on the causative agent; in which viral fungal is less severe and bacterial meningitis is more severe leading to *Neisseria Meningitidis, Streptococcus pneumoniae,* and *Haemophilus influenze*. *Neisseria Meningitidis,* a human pathogenic bacteria, is responsible for one-third of all bacterial meningitis cases in the world. *Neisseria meningitidis* causes life-threatening meningococcemia when it infects blood and when it crosses the blood-brain barrier mixes with the cerebrospinal fluid (CSF) and becomes highly lethal. Invasive meningococcal disease (IMD) is the evolutionary dead end for this pathogen, since the ability to transmit the disease to other hosts will be lost after entering into the blood stream or central nervous system. This organism attacks people irrespective of age, but different vaccines are required for people of different ages. Notably, the cases have greatly decreased in Europe and North America with the introduction of conjugate vaccines (MenC and MenACWY) and in the sub-Saharan Africa with the introduction of MenAfriVac. The invention of conjugate vaccines not only protected from getting infected but put an impact on carriage as well. This helped in creating indirect protection to the unvaccinated population. Taking all these into consideration, immunization with new generation vaccines based on the age classes (such as infants to 1 year, adolescents, young adults and old age people) will have great impact on the disease and carriage. Hence there could a tremendous decrease of the incidence of meningococcal disease globally.**

Keywords: **Neisseria meningitidis, immunity and Neisseria meningitidis vaccines, epidemiology of Neisseria meningitidis.**

1. INTRODUCTION

Epidemiology is the branch of medicine that deals with the incidence, distribution, control, and prevention of diseases related to health. The history of epidemic diseases shows the first step has been to reduce the spread of the disease in populations. *Neisseria Meningitidis*, a human pathogenic bacteria, is responsible for one-third of all bacterial meningitis cases in the planet. *Neisseria meningitidis* causes life-threatening meningococcemia when it infects the blood and meningitis; and when it crosses the blood-brain barrier mixes with the cerebrospinal fluid (CSF) which is responsible for high lethality. **[1] [2]** Meningitis is an acute infection—i.e., inflammation of meninges—the protective membrane covering the brain and spinal cord. The causative agent primarily is *Neisseria meningitidis.* It is an aerobic, Gram-negative diplococcus bacteria and humans are the only reported host of this bacteria. The disease spreads from persons to persons by coming in close contact with respiratory secretions. The mechanism and reason that causes transition from asymptomatic carriage to invasive disease is still not completely understood; some factors, such as genetic and capsular structure of pathogenic strains are considered to play significant roles. **[3]**

This pathogen has the ability to infect people of almost all the age groups and hence the entire population comes under risk. The infection largely affects third-world countries such as Africa, however, even North America and Europe where standard of living is high, people have become victim of this dangerous epidemic. The disease progression is very rapid.

Of the 13 clinically significant serogroups of this organisms—A, B, C, D, E29, H, I, K, L, W135, X, Y, Z—that depend on the antigenic structure of their polysaccharide capsule; A, B, C, X, Y, and W-135 are the major pathogenic strains. Almost ten percent of the healthy population is carrier of this organism, and if the infected people are not treated on time, mortality touches 100%.**[4]**

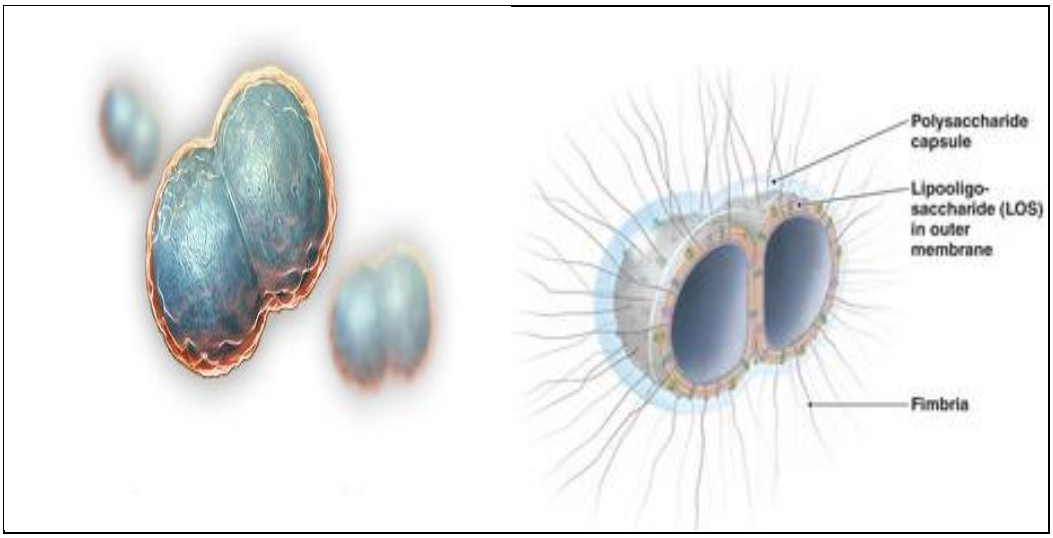

Fig-1: Neisseria meningitidis – Encapsulated

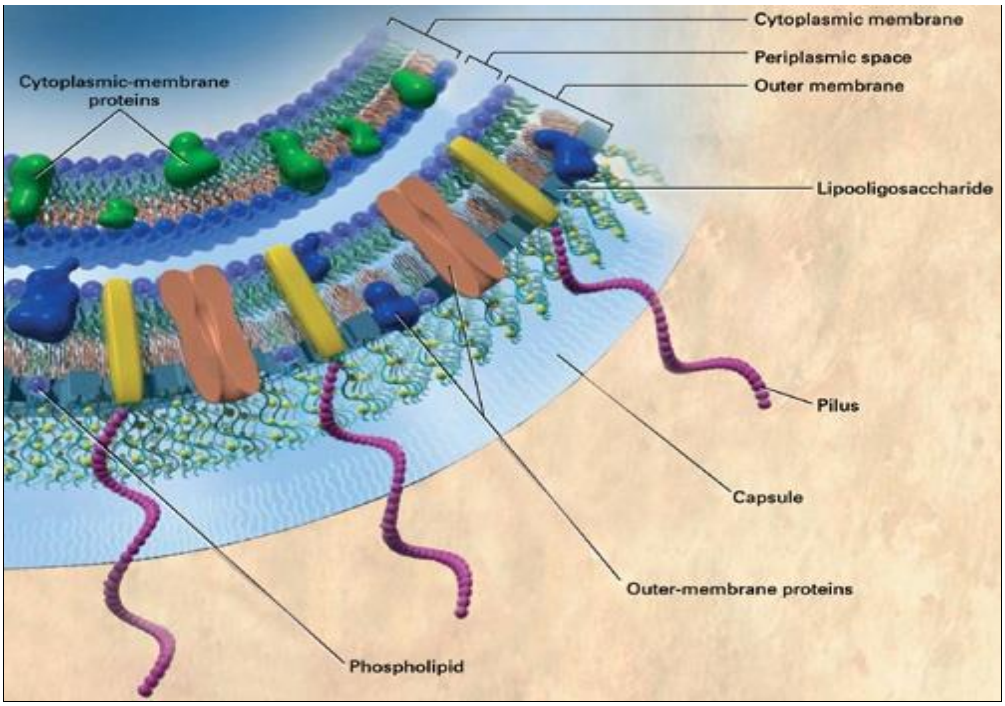

Fig-2: Membrane structure of *Neisseria meningitidis*

2. INFECTION, SYMPTOMS AND TREATMENT OF *NEISSERIA MENINGITIDIS*

The microorganism is reported to infect more frequently during winter and spring seasons, which are rather dry. This condition follows a combination of cold night and dust winds, which facilitate the outbreak of upper respiratory tract infections **[5]**. Five to ten percent of the population may be carriers of *Neisseria meningitidis* at any point of time **[6].** The infection transfers via respiratory system by sneeze, coughs, kissing and nearby breathing. The organism naturally colonizes the posterior nasopharynx, at the back of the nose and throat, without causing symptomatic disease. It attaches to the host cell using Trimeric Autotransporter Adhesins (TAA), which are proteins found on the outer membrane of the bacteria and causes infection and from there it flows into the blood stream to the meninges around the brain. **[7]**

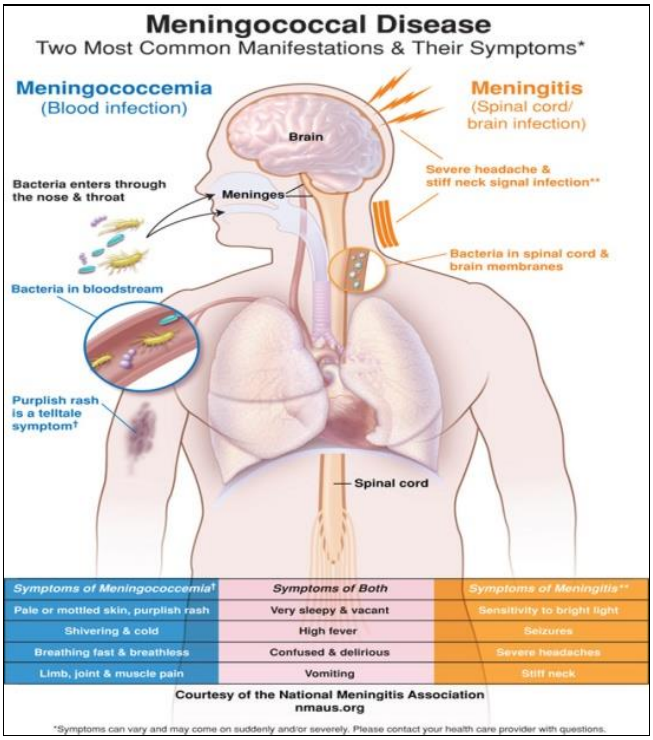

Fig-3: Infection and symptoms

Early symptoms of a bacterial meningitis infection may be fever, malaria, vomiting, headache, neck and spine stiffness, exaggerated reflexes or any combination of them. Advanced meningitis shows minute hemorrhages in the skin (petechiae), especially in the areas subjected to high pressure such as the back or waistline which may lead even to delirium and coma. Ten to fifteen percent of the survivors experience significant morbidity in the form of neurological sequel such as hearing loss, speech disorders, loss of limb mobility, mental retardation, and even paralysis **[6].** Early treatment of meningitis was done by administrating antibiotics such as penicillin, ampicillin or chloramphenicol, but the emergence of drug resistant strains reasoned to think of inventing more effective vaccines for meningitis.

Age-wise variance of *Neisseria meningitidis infection:*

Children <1 year of age are at a higher risk of developing meningococcal disease, because their immunity is low. Also immunosuppressed subjects (like sickle cell anemia, thalassemia, organ transplant, cancer, HIV infection, diabetes, congenital immune deficiencies etc.) are at increased risk. Another age category, which is under high risk, is that of adolescents and young adults (of 15-25 age group, because of their habits and behavior like interpersonal contacts etc.) and travelers who stay for a long duration in the epidemic areas. European incidence is reported to have decreased since 2008, but higher rate of infection has been registered in Lituania and UK. **[8]**. The most relevant serogroup whose reported cases were high among children <1 year of age is MenB. According to the 2012 report, the rate of infection in <1 year of age was three-fold than of the age group 1-4 years children. Report on MenC cases show high infection rate among young adults and adults (25-44 age group), whereas MenY cases were mostly reported in >65 year old subjects. **[9]**

Epidemiology of *Neisseria meningitides:*

Meningitis can be bacterial, viral, fungal parasitic, and non-infectious meningitis depending on the causative agent. Of these types, viral and fungal are less severe and can get recovered by the self immunity. The causative agent of noninfectious meningitis may be cancer, drug addiction, head injury, and brain surgery etc. A parasite called Naegleria fowleri, though a very rare type of parasite, causes primary amebic meningoencephalitis (PAM). This brain infection progresses rapidly. Even though the symptoms are similar in each type, the treatment and severity of the disease differs depending on the cause, hence accurate diagnosis is crucial to get the right treatment **[10]**. Bacterial meningitis is severe than all others and leads to diseases such as *Neisseria Meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenze*.. All three of these organisms are respiratory pathogens. It was first described by Swiss physician Gaspard Vieusseux in 1805 during an outbreak with 33 deaths in the vicinity of Geneva, Switzerland, and was first isolated by Austrian pathologist and bacteriologist Anton Weichselbaum in 1887 from patients infected by this organism. **[11]** .

The disease affected areas were grouped into high risk (African meningitis belt), moderate risk (European and African regions, Australia) and low-incidence countries (that include several countries from Europe and the Americas). **[12]** The 'meningitis belt', with an estimated population of 300 million, includes the countries such as Gambia, Senegal, Guinea-Bissan, Guinea, Mali, Burkina Faso, Ghana, Niger, Nigeria, Cameroon, Chad, Central African Republic, Sudan, South Sudan, Uganda, Ethiopia, Kenya, and Eritrea are at high risk of meningitis. High and moderate-incidence countries were under strict vigilance and given priority for vaccine intervention than low risk countries **[13].** *Neisseria meningitidis* serogroups B and C are the most common causes of disease in Europe, the Americas, Australia, and New Zealand; serogroup A is the main cause in Africa and Asia; although there happened an outbreak of W-135 serogroup in the years 2000 and 2001 among the Hajj pilgrims. Serogroup A caused the largest outbreak in 1996 which claimed more than 20,000 deaths. **[14]**. Figure-1 shows the disease affected areas globally which have been grouped into high risk (African meningitis belt), moderate risk (European and African regions, Australia) and low-incidence countries.

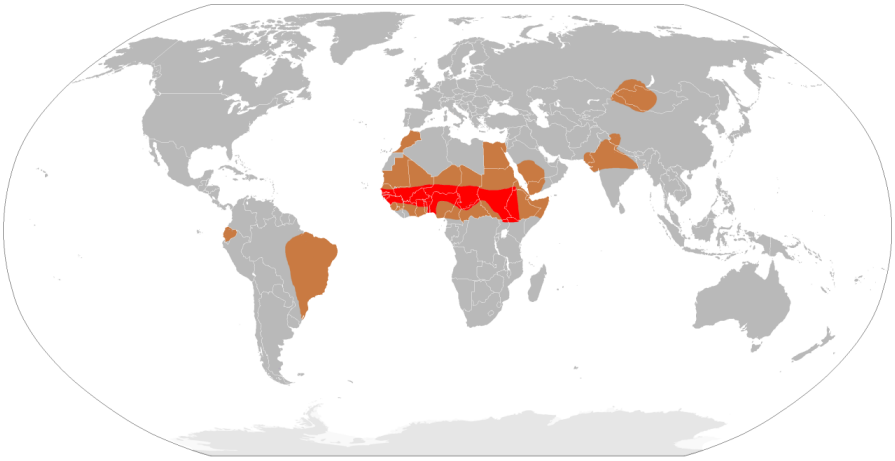

Fig-4: The areas highlighted in red are the Meningitis belt, in brown are the high risk regions of epidemic, while in gray are the places with a sporadic cases only (2004).

(Source: http://www3.chu-rouen.fr/Internet/services/sante_voyages/pathologies/meningite/)

Some of the developing countries show a frequent epidemic of meningitis among which the serogroups isolated were A, B, C, W135, and Y (Fig-5). Serogroups B and C are common in Europe and the Americas, whereas serogroups A and W135 are the main causes in the African meningitis belt and Far East. **[15]**

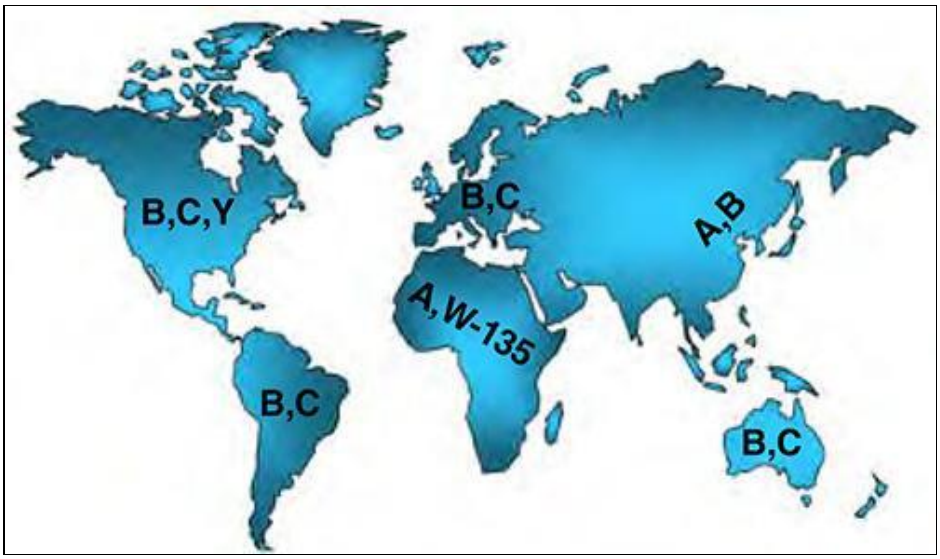

Fig-5: The distribution of Neisseria meningitis serogroups across the globe.

(Source: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/acs-dcc-4/gfx/figure1-eng.jpg)

However, *Neisseria meningitidis* serogroups B and C are the most common causes of this disease in Europe, the Americas, Australia, and New Zealand, while serogroup A is the main cause in Africa and Asia. Outbreak of W-135

serogroup occurred in the years 2000 and 2001 among the Hajj pilgrims. Serogroup A caused the largest outbreak in 1996 that claimed more than 20,000 deaths. During the period 2010-2016, MenC infection in clusters were reported in the United States: in New York City during 2010-2013, Los Angeles County during 2012-2014, and Chicago during 2015−2016. Also in Europe cluster infection occurred in Berlin (2012–2013) and in 2014 in Paris. **[16] [17]**

Immunity and *Neisseria meningitidis* vaccines:

History shows immunization is the most efficacious preventive method against meningococcal disease. The vaccine availability reduced the epidemic rate of the existing serogroups, but it bypassed with the emergence of other serogroups. The polysaccharide vaccines against A, C, Y, and W-135 has been available from 1970-1980s. Later, conjugate vaccines have been introduced, which differ from polysaccharide vaccines, that conjugate vaccine elicit a T-dependent immune response with the production of antibodies and immune memory. Newborns also can be vaccinated with conjugate vaccines.

Even though polysaccharide and conjugate meningitis vaccines are available in the market, their high cost makes them unaffordable by the common people. Although new vaccines are being manufactured, meningococcal infections are steadily increasing in both developed and developing countries, because of the absence of universal vaccine coverage and antibiotic resistance is more common. **[18]** Introduction of a monovalent MenA vaccine (MenAfriVac™) brought the disease under control and the reported cases of MenA have been found negligible, whereas significant rate of cases and death were reported on MenX and MenW in the year 2012. The increasing demand due to the outbreak of Meningitis caused by C and W-135 serogroups in Africa and unavailability of sufficient vaccines highlighted the need of developing of a multivalent conjugate vaccine at an affordable cost. Table-1 shows the available meningococcal vaccines in the market.

Table – 1: Available vaccines against different serogroups of *Neisseria meningitidis*

Trade name	Vaccine Target	Type of vaccine
TRUMENBA®	Meningococcal Group B Vaccine	sterile suspension composed of two recombinant lipidated factor H binding protein (fHBP) variants from Neisseria. meningitidis serogroup B
Bexsero®	Meningitis B serogroups	multi-component MenB vaccine / recombinant, adsorbed
Menhibrix	Meningococcal (C,Y) and Hib	Conjugate Vaccin/ Tetanus Toxoid carrier protein
Nimenrix™	Serogroups A, C, W135, and Y	Conjugate vaccine/ tetanus toxoids carrier protein
Menveo®	Serogroups A, C, W135, and Y	Conjugate vaccine / CRM197 carrier protein
MenAfriVac™	Serogroup A	Conjugate vaccine
Menectra®	Serogroups A, C, W135, and Y	Conjugate Vaccine / Diphtheria Toxoid
NeisVac-C™	Serogroup C	Conjugate Vaccine / Diphtheria Toxoid
Meningitec®	Serogroup C	Conjugate vaccine / CRM197
Mencevax®	Serogroups A, C, W135, and Y	Polysaccharide vaccine
NmVac4	Serogroups A, C, W135, and Y	Conjugate vaccine/ DT
Menomune® (MPSV4)	Serogroups A, C, W135, and Y	Polysaccharide vaccine

3. CONCLUSION

Immunization with new generation vaccines based on the age classes (ranging from infants to 1 year, adolescents, young adults and to old age people) will have great impact on the disease and carriage, which can result in an effective control on the incidence of meningococcal disease globally. Meningococcal cases have decreased during the last decade because of the implemented immunization programs with the conjugate vaccines against the serogroups A, C, Y, and W-135. Vaccine against serogroup B also has been introduced recently. These vaccines are safe and elicit a long-lasting immune response in all age classes and induce herd immunity. Hence meningococcal immunization programs against this deadly disease should be a public health priority globally.

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