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Advancements and Challenges in Meningococcal Disease Management and Prevention

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Abstract

This research offers detailed insights into managing and preventing meningococcal disease, highlighting *Neisseria meningitidis* and *Neisseria gonorrhoeae* as key pathogens. It focuses on the epidemiological diversity and classification of meningococcal serogroups, along with their worldwide distribution. A significant portion of the study is dedicated to advancements in vaccination, especially conjugate and protein-based vaccines, which have markedly enhanced prevention. The study examines the transmission and carriage mechanisms of *N. meningitidis*, emphasizing its carrier state and potential to cause severe diseases like meningitis and sepsis. It also explores virulence factors such as the polysaccharide capsule, lipooligosaccharide (LPS), and Type IV pili, and their contribution to disease pathogenesis. Additionally, it discusses nasopharyngeal epithelium colonization and the host's immune response role. The research ultimately highlights the crucial need for ongoing surveillance, vaccination, and international public health initiatives in effectively addressing meningococcal disease. The research provides valuable insights into the management and prevention of meningococcal disease. It emphasizes the critical role of vaccination, the need for ongoing surveillance, and the importance of global public health initiatives to mitigate the impact of this disease.

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1. Introduction

Neisseria is a large genus of obligate human pathogenic bacteria that was first described and named in 1879, by Albert Neisser, a German bacteriologist who identified its first species, *Neisseria gonorrhoeae*, while in 1887, Anton Weichselbaum, an Austrian bacteriologist, discovered what was initially known as Diplococcus intracellular is meningitidis, later reclassified as *Neisseria meningitides* [1]. Presently, this genus encompasses over 25 species, all Gram-negative, aerobic, and positive for catalase and oxidase tests, typically presenting in diplococci form. Of these, only *N. meningitides* and *N. gonorrhoeae* are recognized as pathogenic [2].

The commensal strains within *Neisseria* genus have also been associated with different opportunistic infections. Each species in this genus adheres to specific mucosal epithelial tissues in their hosts, and while these species are found in multiple animals, involving humans, both *N. gonorrhoeae* and *N. meningitidis* are exclusively considered pathogenic bacteria. Despite their high genetic similarity, these two pathogens differ significantly in their colonization sites and the diseases they cause *N. gonorrhoeae*, primarily located in the urinary tract, responsible for gonorrhea, and highly prevalent transmitted sexual infection, on the other hand, *N. meningitidis*, commonly found in the upper respiratory tract alongside commensal bacteria, often exists in a harmless carrier state but can cause severe conditions like bacterial meningitis and sepsis [3].

Our study aims to investigation the management and prevention of meningococcal disease, emphasizing the importance of *N. meningitidis* and *N. gonorrhoeae* as a key pathogens. It will examine the disease's epidemiological diversity and worldwide

spread, focusing on classification of serogroups and their effects. A major goal is to evaluate progress in vaccination, especially the influence of conjugating and protein based vaccines on prevention efforts. This research will explore how *N. meningitidis* transmits, its virulence factors, including colonization of the nasopharyngeal epithelium and interaction with the immune system, contributing to disease pathogenesis. The aims of the study is to highlight the importance of surveillance, vaccination programs, and global health initiatives in reducing meningococcal disease.

2. Classification

Meningococcal bacteria can categorized into many serogroups, determined by the makeup of their polysaccharide capsules. However, there are 13 serotypes of meningococcus, six types predominantly linked to caused diseases (A, B, C, W-135, X, and Y) which are depending on their composition polysaccharide capsular antigen, each distinct agglutination that responds to a specific serum [4].

Collectively account for more than 90% of meningococcal disease cases globally. These serogroups are further divided into serotypes and serosubtypes, which are based on the variations in the porin proteins (PorA or PorB) found with their outer membranes, and according to the structure of their lipopolysaccharides (LPS) in immunotypes. In the USA, the majority MM cases are occasioned by both serogroups B and C, while serogroup A is more predominantly responsible in Asia and Africa [5].

In addition, there were significant epidemiologically variations among different countries of the world in the study of meningitis diseases. Furthermore, using a genetic method known as multilocus sequence typing (MLST), meningococcal isolates can be categorized into clonal groups or complexes (CCs). This method relies on identifying allelic variations (sequence types, STs) in seven essential housekeeping genes, providing valuable insights into epidemiological trends and clonal spread. To date, 46 CCs have been identified, and 41 of these have been associated with invasive meningococcal disease [6].

3. Growth and Identification of *Neisseria meningitides*

N. meningitidis, the Gram-negative bacterium responsible for meningococcal meningitis (MM), it is an encapsulated bacteria, aerobic diplococcus which can grow and be cultured on different enrichment media like trypticase soy agar, blood agar, Mueller Hinton and chocolate agar with kidney or a coffee bean shape. The optimal condition of growth is carried out at 37ºC with (5-10% CO_2). Bacterial colonies are oxidase positive which is confirmed by carbohydrate reaction (usually glucose and maltose, but not lactose and sucrose) [7]. Figure 1 and Figure 2

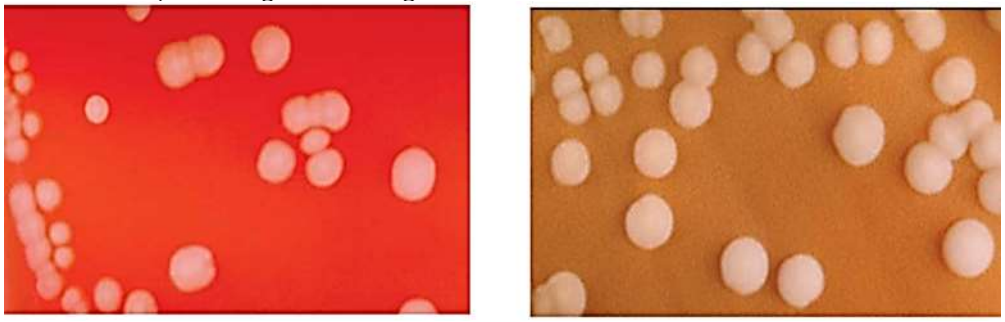

Figure 1. Left: Growth of *N. meningitidis* colonies on blood agar

right: Growth of *N. meningitidis* colonies on chocolate agar [7]

4. Transmission and carriage

About 10% of humans are asymptomatic carriers of *N. meningitides* [8]. The transmission of a disease requires directly contact from person-to-person or by exposure to the respiratory droplets. Respiratory drops are exhibited by drying or wrapped with polysaccharide capsules, so their carriage from person to person requires close contact. The primary habitat for these bacteria is the upper respiratory tract, they are also found in mucosa membrane, urethra, anus, dental plaque urogenital mucosa, and eyes [9]. Meningococci carriage occurs typically through saliva droplets among asymptomatic carriers in close contact. Once established, these bacteria can remain in the nasopharynx for many months. However, invasive disease is rare, with illness usually developing within 1 to 14 days after colonization [10].

Adults and Adolescents exhibit a high rate of carriage of *N. meningitidis*, it is newborns and even children between the ages of 1 to 4 who are most at risk for invasive disease. The prime reason for the high-hazard development of disease is due to immature cellular and humoral immune systems in newborns. In addition, adolescents can increased risk of disease which may be due to a higher rate of carriage. The other factors, including overall health, gender, smoking habits, and socio economic status, also are influence both disease susceptibility and carriage [11].

Other molecular techniques were used to characterize *N. meningitidis* , isolates have revealed insights into the genetic dynamics of these bacteria. Our studies show that the clonal complexes (CCs) were associated with invasive meningococcal disease represent only a small subset of the strains found in the carriers [12]. These disease linked CCs are relatively homogeneous and also limited in number, where as carriage isolates exhibit greater genetic diversity. It is noted that many carriage isolates do not have a capsule, which may aid their ability of bacteria to colonize the human nasopharynx and evade immune detection. Genetic diversity within carriage isolates plays an important critical role in the epidemiology of disease, as a co-colonization with pathogenic strains during carriage and can facilitate genetic recombination and capsule switching, potentially triggering the onset of the disease [13].

5. Disease

Although there's a high rate of meningococcal carriage, the progression to invasive disease is uncommon [14]. For the bacteria to cause an illness, they must first adhere to and then breach the mucosal barrier, withstand the host's immune response, replicate, and persist in the bloodstream. The development of the disease is influenced by a combination of meningococcal virulence factors, environmental factors within the host, and the effectiveness of the host's immune defense. Initial symptoms of meningococcal disease often mimic those of the flu, including high fever, muscle illness, chilliness, and leg and lower back pain, making early diagnosis and treatment difficult. Without prompt treatment, the disease can rapidly advance within a few hours to sepsis or meningitis onset of initial symptoms [6].

Over 50% of meningococcal diseases lead to Meningitis [15]. Bacteria breach the brain via the blood barrier and invade subarachnoid space, their uncontrolled division is facilitated by the absence of adequate humoral and cellular immune responses. The presence of endotoxins may trigger to release of cytokines pro inflammatory that compromise the integrity of blood brain barrier. Although these cytokines attract neutrophils and some other immune cells to combat this bacteria, they inadvertently heighten inflammation in the central nervous system, exacerbating the infection's severe symptoms. This inflammation leads to tissue swelling and can increase cerebral perfusion and intracranial pressure [16].

Symptoms of this condition are characterized by fever, a distinctive rash, low blood pressure, shock, and the onset of disseminated intravascular coagulation (DIC) leading to failure of multiple organs. In severe instances, necrosis of vascular can occur, and infection within just a few hours Fulminant sepsis can develop. When the bacteria enter blood stream, they start to multiply quickly and liberate substantial quantities of endotoxin, in the form of bubbles. This triggers the activations of the complement system and the production of pro inflammatory cytokines, among other responses, potentially leading to shock [17].

An escalated inflammatory reaction within bloodstream can precipitate a fall in the circulatory and an abnormal coagulation pathway in activation. Patients who develop sepsis, in contrast to those with only meningitis, face a substantially higher mortality rate, ranging between 20 to 80%. Furthermore, survivors of sepsis often endure serious physical and mental disabilities[17,18].

6. Epidemiology

Neisseria gonorrhoeae is an important general challenge of health and represents the second most sexually prevalent bacteria transmitted disease in the world [19]. WHO provides the estimation of annual diagnosis with approximately 106 million new cases in adults, with more additional undetected infections [20]. In the United States, *N. gonorrhoeae* is commonly found to become the second most reported sexually transmitted disease, and over five lakh cases are recorded every year [21]. *N. meningitidis* ranks among the leading causes of meningitis globally, with annual reports of 500,000 to 1,200,000 cases of invasively meningococcal diseases, leading to 50,000 to 135,000 fatalities. The incidence of these cases differs across various seasons and regions. The 'meningitis belt' of a Sub Saharan Africa experiences the highest prevalence, up of 10-1,000 case/100,000 people during the epidemic peak. Historically, serogroup A was the predominant strain in Africa responsible for about 10-20 cases/100,000 individuals in the dry seasons, As of 2009 [19]. However, since the MenAfriVac campaign's launch in 2010, there is a substantial reduce in serogroup A infections in the meningitis belt. This has resulted in an estimated 57% drop in overall cases and a 60% decrease during the high-risk winter months. Conversely, C, W, and X serogroups began to emerge in 2010, with the outbreaks caused by serogroups C and W in 2012 and also 2015 [20]. While South Africa experiences sporadic epidemics, no such outbreaks have been reported in Northern Africa to date. In Asia, serogroup A remains the primary culprit for most diseases, although comprehensive few limited data from the continent [21].

Meningococcal disease is comparatively rare in developed regions, with rates typically under 5 cases per 100,000 people, predominantly involving serogroups B, C, and Y, and usually presenting as isolated incidents [22]. For instance, in 2011, only 0.77 case/100,000 individuals were reported across 29 countries in Europe, mainly attributed to serogroups B (73.6%), C (14.4%), and Y (8.2%) [19]. The implementation of MenC vaccination program has led to a decrease in cases that may be caused by serogroup C. However, there has been a noticeable increase in cases linked to other serogroups [22]. In Sweden, for example, the rate of meningococcal disease has remained relatively stable, with most cases caused by each of serogroups B and C. Notably, there was a significant rise in serogroup Y cases from 2009 to 2013, and serogroup W appeared in 2015. Likewise, there's been

an upsurge in serogroup W meningococcal disease in British, Netherlands, Finland, and even Australia [23,24]. The critical role of effective vaccines in controlling the severe diseases caused by *N. meningitidis* is undeniable.

7. *N. meningitides colonization and virulence*

Neisseria meningitidis is a Gram-negative bacteria that causes invasive disease that is associated with significant mortality and morbidity [1]. For *N. Meningitides* causing invasive disease and survive, it should successfully adapt to the varying environmental conditions of the upper respiratory tract, cerebrospinal fluid (CSF), and bloodstream. Owing to continuous selective pressure in these environments, the bacterium has evolved numerous strategies to evade the host's immune system. Notably, meningococci possess natural competence, allowing them to readily acquire new genetic traits. Key virulence factors contributing to their pathogenicity include capsule polysaccharide, lipopolysaccharide, IV type of pili, and opacity proteins [17] (Figure 3).

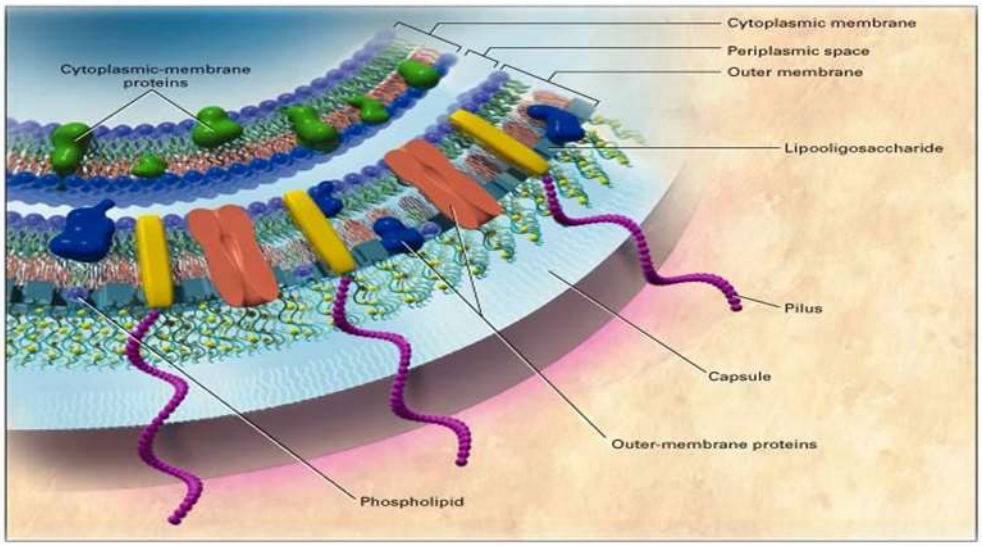

Figure 3. Cross syllabic view of the meningococcal cell membrane [17]

polysaccharide capsules represent a key virulence factor in meningococci, crucial for invasive disease, which is rarely caused by strains lacking this capsule [5]. Among the 13 known meningococcal serogroups, only six are associated with invasive diseases. Four of these serogroups have capsules composed of sialic acid derivatives, with variations in their chemical connections: poly sialic acid in each serogroup B and C, sialic acid in serogroup Y that links with D-glucose, and D-galactose in serogroup W. while capsules in serogroups A and X which contain N acetyl D mannose amine phosphate and N-acetyl glucose amine phosphate, respectively [25].

The capsule also has an important role in the cohesion which aids in the formation of biofilm, changes in the structure of the capsule, and the ability to conceal the membrane bound adhesions aiding for changing and enhance invasion of the host cell [7].

8. Lipooligosaccharide

Previous studies showed that lipooligosaccharide (LPS) is linked to its inflammatory potential phosphorylation process of lipid A in Neisseria, which indicated cytokine in the human monocytes and severity of infections. In *Neisseria meningitidis* LPS, lipid A modification with phosphoethanolamine (PEA) reduces the activity of bactericidal cathepsin G in extracellular neutrophil traps and increases bacterial adhesion with human cells. Additionally, PEA presence on the oligosaccharide of LOS, especially at a specific site on heptose, and expression of sialic acid which found to prevent complement activation in each classical and the alternative methods. [26]

9. Type IV pili

Type IV pili is another key for bacterial adhesion, unique in being present in Gram positive and Gram negative bacteria [27]. They're especially important for the initial attachment of encapsulated meningococci. Beyond just attachment, these pili are also involved in various critical functions such as motility, aggregation, biofilm formation, and natural transformation, aiding

in the bacteria's survival inside the host [19]. Among the 23 proteins linked to Type IV pili, 15 are crucial for their creation, and seven play a role in enhancing their functionality [2].

Type IV pili are thin and flexible filaments, and about 6 nm diameter, projecting a few micrometers from the bacterial outer membrane. Their primary building block is the PilE subunit, which is initially produced with terminal peptide and then transported via the inner membrane by the system. These pili are categorized into two types based on their peptide and protein: the shorter Type Iva, and the longer Type IVb. Type IVa pili exist in both bacteria (*N. meningitidis* and *N. gonorrhoeae*) [14].

Type IV pili forming in bacteria includes critical stages: first, the prepilin is moved via the inner membrane by the Sec system. After, the prepilin peptidase enzyme, PilD, cleaves it. Following this cleavage, and pilus unit was put together moving through the outer membrane, a process depending on PilF cytoplasmic ATPase and secretin PilQ [16]. The successful assembly of Type IV pili also requires the involvement of proteins PilM, PilN, PilO, and PilP [3]. Both forms of gonococcal PilC, namely PilC1 and PilC2, act as adhesins [28]. Figure 4

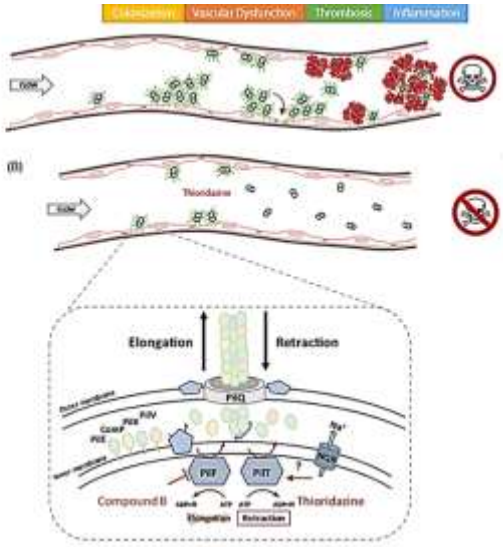

Figure 4. Graphical representation of type IV pili in meningococcal pathogenesis (the role) [28].

X-ray crystallography has provided the structure of the full length of Type IV pilin protein, achieved disassembling intact pilus filaments using some detergent. This process has revealed a standard structure featuring a gently curved 53 amino acid α helix (α1), with its C terminal half embedded in a globular C terminal domain [29].

The α1N, the N-terminal half of the α-helix in Type IV pilins, extends of globular domain, and consists primarily of hydrophobic residues, except for a threonine or serine at the second situation and a consistent glutamate at the fifth. The presence of two helix-disrupting residues, Pro22 and Gly42, common in Type IV pilins of the IVa class, creates bends in α1, contributing to its curvature. Additionally, a glycine at position 14 is also protected. α1N serves two roles in T4P biogenesis: it anchors the globular domain to the inner membrane before the assembly of the pilus, and it binds with neighboring α1Ns in the constructed pilus, forming a staggered helical pattern in the filament's core [28]. The consistently present Glu5 plays a vital role in T4P assembly, as indicated by multiple studies. Models of T4P, partially based on the crystal structure of the full-length pilin subunit PilE from Neisseria gonorrhoeae (Ng PilE), suggest that this residue forms a salt bridge with the positively charged N-terminal amine of its adjacent molecule. This interaction occurs within the predominantly hydrophobic core of the filament [24].

10. Opacity proteins: Opa and Opc

Type IV pili penetrate polysaccharide capsules, which form the outermost layers of *N. meningitidis*, which are widely considered a primary adherence mechanism in fully encapsulated meningococci. Although the capsule partially obscures outer membrane proteins, these proteins still effectively facilitate adhesion to and invasion of eukaryotic cells. This is particularly true for cells with a high density of receptors, a condition that might arise during inflammation or as a result of lateral receptor aggregation [29]. Figure 5

The colonies are opacity associate proteins Opa and Opc are key components of outer membrane proteins in *N. meningitidis*. Opa proteins are characterized by their significant structural variability, with approximately 4 to 5 loci (opaA, B, D, and J) encoding them. These proteins are composed of about eight transmembrane β-strand and about four loops that are exposed on the surface [25].

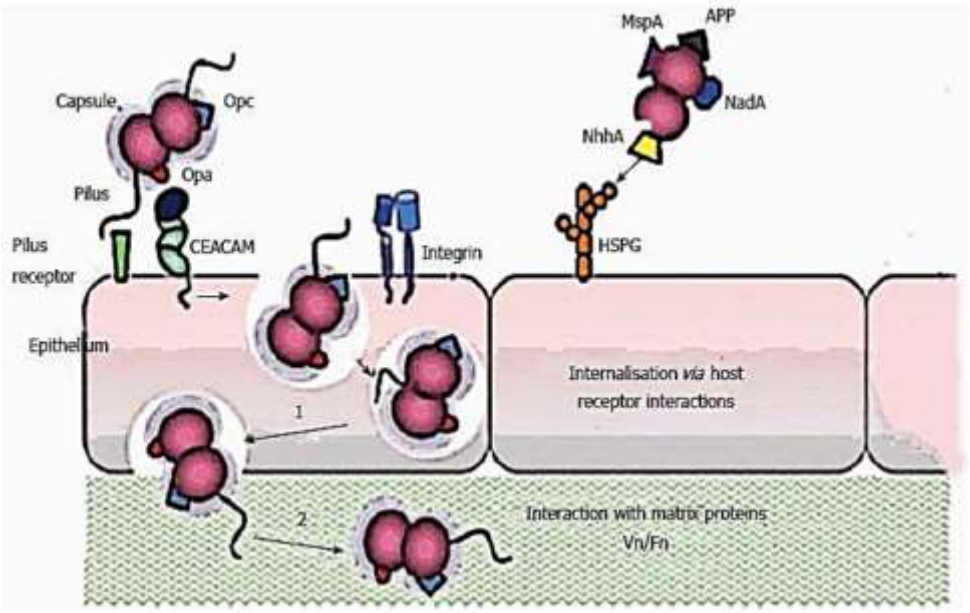

Figure 5. Schematic representation of the interaction mechanisms of *Neisseria meningitidis* with cellular receptors [29]

Opa proteins facilitate close adhesion and invasion into various cell types by activating cellular signaling for the internalization of bacteria. Specific meningococcal Opc, which are encoded by a single gene and distinction from the protein Opa, in addition, they aid in adherence and penetrate by interacting with heparan sulfate, fibronectin, and vitronectin in epithelial and endothelial cells. The Opc serves as a practical equivalent to OpaHS [16].

11. Colonization of the nasopharyngeal epithelium by *Neisseria meningitides*

Neisseria. *meningitidis* spreads between individuals through airborne droplets generated during activities like breathing, speaking, or coughing, or through direct exposure to infected fluids. The primary habitat for *N. meningitidis* is the mucosa of the nasopharynx of humans which is situated in the rear of the nose and above the oropharynx. In this location, these bacteria coexist with the diverse microbial community that experiences ongoing shifts related to age and in response to upper respiratory infections [30,31].

The nasopharyngeal lining consists of two primary types of epithelial tissue: a pluristratified squamous epithelium, which accounts for about 60% of nasopharynx, and a respiratory epithelium [32]. Cells were covered within the respiratory tracked by a dual-layered surface liquid, measuring 10 to 12 micrometers in thickness. This liquid comprises a low viscosity periciliary liquid (PCL) direct contact with cells and a denser and high viscosity mucus layer returning lumen. The latter traps bacteria, snuff particles, and cellular ruins (referred to as outer mucus) [24]. Thus PCL plays a key role in promoting ciliary movement, which in turn enables efficient mucociliary clearance at a rate of approximately 6.9 ± 0.7 mm/min [33].

This mucociliary mechanism, which continuously moves the mucus from the lower respiratory tract to the pharynx for swallowing, and deemed a primary advocate against microorganisms. A mucus layer of commensal bacteria containing a dense gel comprised of mucins that are rich in various antimicrobial agents like lysozyme, IgA, lactoferrin, and other human defenses [34-35].

The mucins belong to the family of about 22 high molecular weight glycoproteins, which are categorized into two types: membrane that associated mucins produced by such epithelial cells, and the gel forming mucins secreted by cup cells submucosal glands. This mucus layer is predominantly made up of MUC5B and MUC5AC in the respiratory tract. Expression of these mucins is closely controlled and reacts to the infection of bacteria as well as the range of the respiratory disease [32].

12. Vaccines against Meningococcal Diseases

To prevent getting meningococcal disease it's necessary to get the vaccine. Vaccination is the most efficient strategy to prevent invasive meningococcal disease (IMD) due to its progression and quick onset, and it also to less associated healthcare costs. Considerable advancements in IMD preservation can achieved through the development of meningococcal vaccines. At first, capsular polysaccharide vaccines targeting serogroups A, C, W, and Y present a few benefits in infants due to poor efficacy,

little duration protection, and loss of immune induction memory. The polysaccharide-conjugate vaccines (MenACWY), which linked the polysaccharide antigen to the carrier protein which was used until this day, addressed these issues, enhancing protection in young children, the most vulnerable group [33]. Additionally, by using these conjugate vaccines have been effective in reducing nasopharyngeal carriage, thereby facilitating were immunogenic induced memory immunity from birth.

Different vaccines were available for this disease against many serogroups and at least the activity was about 85-100% for two years [34].

Two types of vaccines were available:

- Meningococcal ACWY vaccine against A,C,W, and Y serogroups.
- Meningococcal B vaccine against some strains of serogroup B.

Many formulations of the MenACWY vaccine have long been a part of national immunization programs. Developing a vaccine for serogroup B (MenB) was more difficult; however, two active protein-based MenB vaccines are available and provide wide protection.

Meningitis and septicemia, primarily caused by *meningococcus*, pose global health challenges. *Meningococcus* often resides asymptomatically in the nasopharynx of about 10% of adults, increasing to over 25% during adolescence, with humans as the sole reservoir. Invasive meningococcal disease (IMD) mortality can reach up to 10%, but this risk escalates without prompt and adequate treatment [35]. Early detection, effective parenteral antibiotics, and immediate management of complications such as circulatory shock and increased intracranial pressure are critical to improving outcomes.

Currently, Vaccines used against bacteria *Neisseria meningitidis*

1. Polysaccharide Vaccines

Effective vaccines are available for five serogroups of *N. meningitidis* that cause disease (A, B, C, W, and Y). For serogroups A, C, W, and Y, both polysaccharide-based and glycoconjugate vaccines are in use [36]. Polysaccharide vaccines that were currently in use were quadrivalent, incorporating capsule polysaccharides from A, C, W, and Y serogroups. Previously available monovalent targeting only A and C serogroups or trivalent targeting A, C, and W serogroups vaccines have been phased out in favor of the quadrivalent formulations. Mencevax, produced by GlaxoSmithKline, is authorized for use in Europe. These vaccines consist of pure capsular polysaccharides derived from bacteria of the specific serogroup directly and are first deployed during outbreaks and epidemics. Consequently, conjugate vaccines are the predominant type used to prevent infections caused by A, C, W, and Y serogroups of *N. meningitidis* [37].

2. Conjugate Vaccines

Carbohydrate glycoconjugate vaccines leverage bacterial sugars, which are bonded with protein carriers. The process begins with isolating of meningococcal polysaccharide capsule, which is then exposed to acidic hydrolysis to break it down into smaller oligosaccharide fragments. These fragments are further refined through chromatographic techniques to select a specific size range suitable to the vaccine [38]. Primary three carriers of proteins were used including diphtheria toxoid (DT), CRM197 (a modified form of DT with an amino acid substitution at position 197 rendering it non-toxic), and tetanus toxoid (TT). These carrier proteins, derived from *Corynebacterium diphtheriae* and *Clostridium tetani*, are inactivated toxins that play a vital role in eliciting B-cell and T-cell-dependent immune responses, essential for developing long-lasting immune memory [39].

During vaccine assembly, both the oligosaccharides and the protein carriers are chemically altered to introduce reactive groups that facilitate crosslinking under controlled conditions. However, this method introduces a degree of heterogeneity in the vaccine batches, an issue that recent research aims to resolve by standardizing production processes. Meningococcal conjugate vaccines, which can be monovalent, quadrivalent, or combination vaccines, are tailored to fixed groups of age depending on epidemiological insights into the disease prevalence. Their effectiveness is routinely verified through clinical trials [40].

2.1 Conjugate Monovalent Vaccines

Currently, four monovalent conjugate vaccines are licensed to target specific serogroups of *N. meningitidis*. Three of these vaccines are aimed at combating serogroup C: Meningtec and Menjugate, both utilizing CRM197 as a carrier protein, are produced by Pfizer (USA) and GlaxoSmithKline (UK) respectively, while NeisVac-C, which uses tetanus toxoid (TT) as a carrier, is also produced by Pfizer but based in Canada. All vaccines have been assured effective for babies younger than 2 months [41].

In addition, a monovalent cost effective vaccine against serogroup A, MenAfriVac, as its carrier protein, and developed by Serum Institute of India. This vaccine was created in Africa and is a result of a collaborative effort involving U.S. Administration of Food and Drugs. MenAfriVac targets a broader age range, from 1 to 29 years old, and is specially tailored to meet the needs of the regions most affected by meningitis [42].

2.2 Conjugate Quadrivalent Vaccines

Quadrivalent vaccines, which include sugars capsular from 4 serogroups, offer naturally more extensive protection compared to monovalent vaccines. These vaccines also cater to a broader spectrum of age categories. There are three insured

quadrivalent vaccines, each using different proteins. Menveo, produced by GlaxoSmithKline in the UK, utilizes CRM197 as its carrier protein and is effective for various age groups [43].

2.3 Conjugate Combined Vaccines

Menitorix (Hib-MenC-TT) and MenHibrix (Hib-MenCY-TT) conjugated vaccines protect the serogroups of *N. meningitidis*, *Haemophilus influenzae* type b (Hib). A Gram negative bacterium, the major cause of meningitis and pneumonia in children less than five years old and it's the first bacteria for successful conjugate vaccine development. Both Menitorix and MenHibrix include poly-ribo-sylribitol-phosphate, a key of the Hib bacterial capsule. MenHibrix is designed for children aged 6 weeks to 18 months. Menitorix is administered in two doses; the first is intended for infants aged 1.5- 12 months, and the second dose is designed for children from 12-24 months [44].

3. The Outer Membrane Vesicle and the Protein Based Vaccines

Developing glycol-conjugate vaccines for *N. meningitidis* serogroup B has been challenging due to the potential for self-reactivity, as the capsular polysaccharide of this serogroup mimics human neural cell adhesion molecules [45]. Efforts to use modified sialic acids in vaccines have not yet led to licensed products. Instead, the first successful vaccine against this serogroup was based on outer membrane vesicles (OMVs), which include naturally occurring components from the bacterial membrane that can provoke an immune response. In Cuba vaccines were Licensed in 1987, including the VA-MENGOC-BC vaccine and OMVs which were provides coverage against serogroups B and C .

However, subsequent vaccines, Bexsero and Trumenba, have also utilized many advanced techniques from the reverse vaccinology. This approach were involve the identifying potential antigens through genetic analysis and can creating them by using recombinant DNA technology. Bexsero contains multiple recombinant proteins and OMVs from a specific outbreak strain, while Trumenba is composed of variants of protein lipidated recombinant, and provide offering targeted protection against serogroup B [46].

13. Conclusions

Meningococcal disease is a serious illness that causes different cases of meningitis and septicemia and leading to life-threatening complications. As a public health efforts continue to treating this disease, research has shown a clear value in effective management and prevention through their vaccination. Therefore, vaccines considered the first line of defense in reduce the spread of this disease and minimizing severe complications. This article outlines key conclusions related to meningococcal disease and the importance of preventing through vaccination.

1. Importance of Vaccination: Research confirms the critical role vaccines playing toprevent meningococcal disease. Despite the significant success of vaccination programs, disease remains a public health threat in different regions worldwide.
2. Continuous Monitoring: Continuous surveillance is important to monitor the effectiveness of current vaccines and to ensure a rapid response to outbreaks.
3. Global Public Health Initiatives: Regional strategies and effective global and must be performed to alleviate the effect of the disease. While some countries have combined vaccines into their national programs, others enclose vaccination to high-risk groups and travelers.
4. Updating Recommendations: As vaccines continue to develop, the recommendations must be updated regularly to assure better effectiveness and coverage.
5. Vaccine evolution: Continuous working to improve vaccines and provide broader protection against strains of meningococcal bacteria is crucial for controlling of disease.
6. Raising Awareness: Education on the importance of vaccines in combating meningococcal disease should be an essential part of public health strategies.

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15. Conflict of Interest

there are no conflicts of interest.

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التطورات والتحديات في إدارة مرض المكورات السحائية والوقاية منها

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الخلاصة

بينت الدراسة رؤى مفصلة حول السيطرة والوقاية من مرض المكورات السحائية، مسلطة الضوء على المكورات السحائية *Neisseria meningitidis* و *Neisseria gonorrhoeae* كمسببات رئيسية للمرض. وركزت الدراسة على التنوع الوبائي وتصنيف مجموعات المكورات السحائية ، إلى جانب انتشارها في جميع أنحاء العالم. كما ركز جزء من الدراسة على تطور اللقاحات وخاصة اللقاحات المقترنة ، والتي عززت الوقاية من المرض بشكل ملحوظ. و بحثت الدراسة آليات انتقالها وقدرتها على احداث أمراض خطيرة مثل التهاب السحايا والإنتان. فضلا عن امتلاكها العديد من عوامل الفوعة مثل كبسولة متعدد السكريات polysaccharide capsule ، ومتعدد السكريات الدهني (LPS) والنوع الرابع من الشعرة Type IV pili ، ودورها في احداث المرض. فضلا عن ذلك ، تناقش الدراسة استعمار ظهارة البلعوم الانفي ودور الاستجابة المناعية للمضيف. كما سلط البحث الضوء على الحاجة الماسة لمواصلة المراقبة والتطعيم والمبادرات الدولية في مجال الصحة العامة للتصدي بفعالية لمرض المكورات السحائية. يقدم البحث رؤى قيمة حول إدارة مرض المكورات السحائية والوقاية منه. ويؤكد على الدور الحاسم للتطعيم، والحاجة إلى المراقبة المستمرة، وأهمية مبادرات الصحة العامة العالمية للتخفيف من تأثير هذا المرض.