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Review

Meningococcal polysaccharide vaccines: A review

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ABSTRACT

Polysaccharides produced by *Neisseria meningitidis* are pharmaceutically important molecules, and are the active components of vaccines against *N. meningitidis* serogroups A, C, W135 and Y. Effective vaccines based on capsular polysaccharide, polysaccharide conjugates and outer membrane vesicles have been developed for strains expressing capsular polysaccharides that define the sero groups A, C, Y and W135. However, conventional approaches to develop a vaccine for group B strains have been largely unsuccessful. This review focuses on the various aspects of fermentative production of meningococcal polysaccharide from *N. meningitidis*, methods of conjugation for improving the immunogenicity of polysaccharide vaccine, and efficient and cost effective methods for the purification of *N. meningitidis* capsular polysaccharide and outer membrane vesicles. In addition, different analytical techniques for the quantitative determination of polysaccharide vaccine and evaluation of structural integrity of conjugate vaccine have been described.

1. Introduction

Neisseria meningitidis is a common cause of serious bacterial infection around the world. Infants, immunocompromised individuals and young adults living in close quarters are at higher risk for invasive meningococcal disease than the general population (Campbell et al., 2002). Even with antimicrobial therapy and the availability of advanced intensive care, case fatality rates are 5–10% in industrialized countries, and are even higher in the developing world (Jodar, Feavers, Salisbury, & Granoff, 2002). Three bacterial species, *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Neisseria meningitidis*, are responsible for most cases of meningitis occurring beyond the neonatal period. The incidence of *S. pneumoniae* is greatest in infants and children below 2 years old, that of *H. influenzae* in children from 6 months to 2 years of age, and that of *N. meningitidis* in children, adolescents and young adults from 1 to 29 years of age. *N. meningitidis* moreover is the only bacterium capable of generating epidemics of meningitis. Epidemics have been described as early as 1805 in Europe and recognized for more than 100 years in sub-Saharan Africa.

Neisseria meningitidis are Gram negative, oval cocci, 0.6–0.8 μm, occurring typically in pairs, with adjacent sides flattened or concave (Chakraborty, 1996). The *N. meningitidis* capsule is composed of high-molecular-weight anionic polysaccharides (Romero & Outschoorn, 1994). Polysaccharides produced by *N. meningitidis* are medically important molecules, and are the active components of vaccines against *N. meningitidis* serogroups A, C, W135 and Y. Polysaccharide vaccines for prevention of these diseases have been available for many years. However, vaccines based on plain polysaccharides have important drawbacks, as their immunogenicity is age-related, and they fail to elicit booster response upon reinjection (Cadoz, 1998). Polysaccharide–protein conjugate vaccines are much more effective than unconjugated polysaccharide vaccines in young children (Wenger, DiFabio, Landaverde, Levine, & Gaafar, 1999). Effective conjugate vaccines for the prevention of meningococcal disease caused by group C strains have been licensed in UK and in other European countries (Jodar et al., 2002). Lipopolysaccharide released by *N. meningitidis* in spent media can also be used as antigenic components for production of outer membrane vesicle (OMV) vaccine. OMV vaccines have shown good immunogenicity and safety profiles as they induce immunological memory and bactericidal antibodies against homologous strains in all age groups (Gu & Tsai, 1991). Table 1 shows a summary of studies of meningococcal outer membrane protein vaccine.

2. Meningococcal meningitis

2.1. Epidemiology of meningococcal disease

Meningococcal disease is an endemic as well as worldwide epidemic illness. *N. meningitidis* is a common inhabitant of the mucosal membranes of the human nasopharynx, where it usually lies as a harmless commensal. Up to 5–10% of the population may be asymptomatic carriers in non-epidemic settings. Most cases are acquired by person-to-person contact through aerosol droplets or contacts with respiratory secretions from asymptomatic carriers. A small minority of those who become infected eventually will develop an acute inflammation of the meninges.

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Table 1
Summary of studies of meningococcal outer membrane protein vaccines.

Year of vaccination	Vaccine strain and formulation	Location (population vaccinated)	Age	Percent efficacy (95% CI)
1987–1989	B:4:P1.15 C PS/alum	Cuba (106 000)	10–14 years	83 (42–95)
1989–1990	B:4:P1.15 C PS/alum	Sao Paolo, Brazil (2.4 million)	3–23 months 24–47 months 4–7 years	−37 (−100 to 73) 47 (−72 to 84) 74 (16–92)
1990	B:4:P1.15 C PS/alum	Rio de Janerio, Brazil (1.6 million)	6–23 months 24–47 months 4–9 years	41 (−96 to 82) 14 (−165 to 72) 71 (34–87)
1987–1989	B:4:P1.3 C PS/alum	Iquique, Chile (40 800)	1–4 years 5–21 years	−39 (−100 to 77) 70 (3–93)
1988–1991	B:4:P1.7,16 alum	Norway (171 800)	14–16 years	57 (28–NR)

In industrialized countries, annual attack rates of meningococcal disease average 1–3 per 1, 00,000 of population. The highest incidence is in children under the age of 5 years, with a secondary peak in teenagers and young adults. Case fatality rates in children under 5 years are about 5%, whereas rates of up to 25% are seen in teenagers and adults (Harrison, Pass, & Mendelsohn, 2001). Some groups in general populations, such as university students living in dormitories, or those using catered dining facilities are at several fold higher risk than others of similar age. Additional risk factors include alcohol consumption, smoking and viral respiratory infections such as influenza. Individuals with complement deficiencies, hyposplenism or other forms of immunosuppression are also at increased risk of developing meningococcal disease.

Neisseria meningitidis can be divided into 12 groups based on chemically and antigenically distinct polysaccharide capsules. Meningococci are further classified into serogroups and subtypes on the basis of the immunologic reactivity of their PorA and PorB outer membrane proteins, respectively. Five groups, designated A, B, C, Y, W135, account for virtually all disease-causing isolates. Table 2 illustrates the occurrence of different serogroups with respect to countries (Jodar et al., 2002).

2.2. Clinical manifestations of meningococcal meningitis

Fever and chills, intense headache, stiff neck, vomiting, lethargy or drowsiness or irritability characterizes acute meningitis. Systemic meningococcal disease carries a significant risk of death. Despite antimicrobial therapy, 10% of patients die, typically within 24–48 h of onset of symptoms. Another 10–20% of survivors are left with permanent sequelae such as neurological disorders or sensorineural deafness. When meningitis follows hematogenous dissemination of *N. meningitidis,* the disease usually presents as an acute illness of 1–3 days following a short latency period dominated by cold like symptoms. Frequency and severity of the main clinical manifestations varies with serogroups and clones of *N. meningitidis* and is also influenced by age and immunocompetence of patients (Rang, Dale, & Ritter, 1995).

2.3. Therapeutic treatment and preventive measures of meningococcal meningitis

Due to rapidity and severity of the disease urgent measures must be taken for any patient displaying signs of meningococcal infection. Treatment should be initiated immediately, before diagnostic conformation. Isolation of the patient is not necessary. Treatment of meningococcal disease has two facets: antibiotic therapy and supportive care to handle systemic problems and avoid further complications.

Presently, a range of antibiotics may be used for the treatment including penicillin, ampicillin, chloramphenicol and ceftriaxone. Under epidemic conditions in Africa, oily chloramphenicol is the drug of choice but has adverse reactions like aplastic anemia, hypoplastic anemia, agranulocytosis, thrombocytopenia, anaphylaxis, gray baby syndrome, pseudomembranous colitis, optic neuritis and blurred vision. Supportive care is usually complex and demanding, and must be specifically adapted to the case. Close contacts of all persons with invasive disease, whether sporadic or in an outbreak, are at high risk and should receive chemoprophylaxis with in 24 h of diagnosis of the primary case. Prophylaxis is best ensured through administration of a few specific antiinfective drugs, which eliminate nasopharyngeal carriage. Rifampicin is the drug of choice (Satoskar & Bhandarkar, 1993). Rifampicin has adverse reactions such as nausea, vomiting, abdominal pain, diarrhea, skin rash, headache and pain at injection site (Simmons, Jones, & Calder, 2000). Vaccination is generally recommended for the following groups who are at increased risk for meningococcal disease (Jodar et al., 2002).

- People involved in mass concentrations, movements or schools (military, refugees, *etc.*)
- College students
- Travellers to hyper endemic and epidemic areas
- Individuals with health risks (anatomic or functional asplenia, *etc.*)
- Pathological laboratory staff concerned with blood or serum sample testing

2.4. Cell wall structure of N. meningitidis

The inside or cytoplasm of the meningococcus is surrounded by a cell envelope consisting of three layers, an inner layer called the cell membrane, a middle layer composed of peptidoglycans, and an outer layer called the cell wall (Fig. 1). The cell wall is made up of sugar-like molecules (lipopolysaccharides or LPS) and outer membrane proteins (OMPs), which are linked together to form a mesh or sheet, giving the bacterium its shape. The OMPs enable the organism to interact with and adhere to host cells and also act as

Table 2
Occurrence of different meningococcal serogroups with respect to countries (Jodar et al., 2002).

Group	Predominance in countries	Other remarks
A	Sub-saharan African countries, China	Incidence rates up to 30 per 100,000 in countries such as Niger
B	Norway, Netherlands, Germany and Denmark	50–90% Cases in Europe. Highest in infants less than a year old in all countries
C	Czeck republic, Slovakia, Greece, Republic of Ireland, Spain and UK	Common in teenagers and young adults
Y	USA	Capsular group accounting for 1/3rd of cases
W_{135}	–	Common in Hajj pilgrims