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Review

A review of vaccine research and development: Meningococcal disease☆

Marc P. Girard[a,*], Marie-Pierre Preziosi[b,1], Maria-Teresa Aguado[b,1], Marie Paule Kieny[b,1]

[a] *University Paris 7, 39 Rue Seignemartin, FR-69008-Lyon, France*
[b] *Initiative for Vaccine Research, World Health Organization, 20 Ave Appia, CH 1211, Geneva 27, Switzerland*

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Abstract

This paper reviews the current status of research and development of vaccines against meningococcal disease due to *Neisseria meningitidis*, a major cause of severe meningitis and septicemia with epidemic potential. While five serogroups (A, B, C, Y, and W135) are responsible for most of the disease, Group A remains unique in its ability to cause large scale epidemics mainly in Africa but also in Asia. The majority of cases in Europe and America are due to Groups B and C. The successful experience with Hib and pneumococcal conjugate vaccines has paved the way for the development of polysaccharide conjugate vaccines for the prevention of meningococcal disease. Widespread vaccination with Group C conjugate vaccines now in use in several European countries indicates that these vaccines are immunogenic, induce immunological memory, reduce colonization and provide herd immunity to the general population. A monovalent group A conjugate vaccine being developed at an affordable price, offers hope for the elimination of large epidemics in African countries. Multivalent (A, C, Y, W) conjugate vaccines are being developed, and one has already been licensed. However, effective global prevention of meningococcal disease will not be achievable without the development of a vaccine against Group B meningitis, for which outer membrane protein vaccines are under development.

Keywords: Meningitis; *Neisseria meningitidis*; Vaccines; Capsular polysaccharide; Glycoconjugate; Reverse vaccinology

Contents

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* Corresponding author. Tel.: +33 478 746 531.
E-mail addresses: marc.girard36@wanadoo.fr (M.P. Girard), preziosim@who.int (M.-P. Preziosi), aguadom@who.int (M.-T. Aguado), kienym@who.int (M.P. Kieny).
[1] Tel: +41 22 791 35 91.

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1. Introduction

Central nervous system infections, including bacterial and viral meningitis, are major causes of morbidity and mortality. Bacterial meningitis remains a serious threat to global health, accounting for an estimated annual 500,000 cases worldwide with at least 50,000 deaths and as many cases of neurological damage [1]. It has been estimated that in developing countries such as The Gambia, 2% of all children born will die of meningitis before they reach 5 years of age [2]. Even with antimicrobial therapy and the availability of sophisticated intensive care, case fatality rates remain at 5%–10% in industrialized countries, and can reach 20% in the developing world. Between 10% and 20% of survivors develop permanent sequelae such as epilepsy, mental retardation or sensorineural deafness.

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 small infants and children less than 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. Diagnosis of the etiological agent generally rests on Gram stain and culture of cerebrospinal fluid (CSF), but rapid tests based on latex agglutination, stick chromatography immunodetection, multiplex PCR or DNA microarrays are progressively been implemented. The introduction of *H. influenzae* type b (Hib) conjugate vaccines in many countries for routine immunization has nearly eliminated invasive Hib disease in those countries. *N. meningitidis* and *S. pneumoniae* have therefore now become the commonest cause of bacterial meningitis in the world. Meningococcal disease is a global problem that occurs in all countries. In the few surveys done in sub-Saharan Africa, *S. pneumoniae* accounted for about 20%–30% of meningitis cases, whereas *N. meningitidis* was responsible for 60%–65% of cases. *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.

All these pathogens possess a cell surface polysaccharide (CPS) capsule, which prevents activation of the complement by cell surface bacterial proteins and inhibits phagocytosis and bacterial killing, but which also can serve as the antigen of choice for the development of preventive vaccines. They also are characterized by their propensity to colonize the nasopharynx in a harmless way, from where they can invade the host and cause silent bacteraemia or overt infections, such as otitis media, pneumonia, or meningitis.

Among the elderly, pregnant and immunocompromized patients, additional pathogens can cause meningitis, such as *Listeria monocytogenes*, a Gram positive rod that causes infection in immunocompromized persons and pregnant women and *Cryptococcus neoformans*, which has become an important cause of meningitis among immunocompromized patients. Neonatal meningitis is a distinct clinical entity, frequently caused by *Escherichia coli* or group B streptococci. Other pathogens such as *Mycobacterium tuberculosis*, *Treponema pallidum* or *Borrelia burgdorferi*, the causative agent of Lyme disease, may also present as aseptic meningitis. Viruses also cause meningitis, including coxsackieviruses and echoviruses, or, less frequently, cytomegalovirus, herpes simplex virus and HIV.

This review will focus on vaccines against meningococcal disease due to *Neisseria meningitidis*, which can cause severe meningitis and septicemia and which is unique among cases of meningitis for its ability to cause large scale epidemics [3,4]. The development of new vaccines against Hib and *S. pneumoniae* was recently reviewed [5], including the multivalent pneumococcal glycoconjugate vaccines from Wyeth [6–8] that are under development [9].

2. Disease burden

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 a 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. Among the 13 distinct *N meningitidis* serogroups that have been defined on the basis of the immunochemistry of their CPS, groups A, B, C, WI35 and Y are responsible for over 90% of severe meningitis and septicemia. The disease mainly affects infants and young children, with case fatality rates of 10%–15%, mostly in the very young, but also in older children and young adults.

Group A meningococci are characterized by their propensity to cause large-scale epidemics in developing countries but rarely cause disease in North America or in Europe. They are the major cause of both epidemic and endemic meningococcal disease in Africa, with the highest burden of disease occurring in a sub-Saharan area from Senegal to Ethiopia that is referred to as “the meningitis belt”. Meningococcus group A epidemics occur there in irregular cycles every 5–12 years, last for 2–3 years, peaking in March–April at the end of the dry season, and dying out during the intervening rainy seasons. Extensive population travel, such as for the Hajj pilgrimage in Saudi Arabia, facilitates the circulation of virulent strains from country to country, but there still is no satisfactory explanation for the marked seasonality of the disease, nor is it known what starts an epidemic.

The size of these epidemics can be enormous. During the 1996 epidemic in sub-Saharan Africa, around 200,000 cases were reported with 20,000 deaths. Attack rates in epidemic years can be as high as 1000 per 100,000 population, with a case fatality rate between 10% and 20%. Three-quarters of cases occur in individuals less than 15 years of age. Inci-