Background paper on Meningococcal Vaccines
SAGE Working Group

Table of Contents

I. Background on the disease, routes of transmission, risk factors and treatment
   • Pathophysiology ................................................................. 3
   • Routes of transmission .......................................................... 5
   • Signs and symptoms ............................................................. 6
   • Risk Factors ........................................................................ 6
   • Diagnosis ............................................................................ 6
   • Prevention (Chemoprophylaxis and Vaccines) ....................... 7
   • Treatment ........................................................................... 8

II. Epidemiology
   • Definition of epidemics and endemic situations ....................... 9
   • Epidemiology of invasive meningococcal disease at country level ... 10
   • Serogroups, Serotypes .......................................................... 15
   • Carriage .............................................................................. 15
   • Duration of protection of natural disease/ acquisition of natural immunity ................................................................. 16
   • Age specific attack rates ....................................................... 17
   • Use of vaccines .................................................................... 20
   • Replacement disease ............................................................ 22

III. Immunology, safety and effectiveness of meningococcal vaccines
   • Correlates of protection against meningococcal disease .......... 24
   • Field effectiveness of vaccines .............................................. 24
   • Duration of immunity .......................................................... 24
   • Herd protection ................................................................... 25
   • Polysaccharide meningococcal vaccines ................................ 26
   • Conjugate meningococcal vaccines ........................................ 26
   • MenC Conjugate vaccine ................................................... 27
   • Quadrivalent meningococcal conjugate vaccines .................... 27
   • MenA conjugate vaccine ..................................................... 27
   • MenB OMV vaccines ........................................................... 29

IV. Cost effectiveness of vaccine and cost of disease
   • Cost effectiveness of vaccines in Africa ................................... 29
   • Cost of disease and impact on health systems in Africa ............ 30
   • Cost effectiveness of Men C conjugate vaccine ....................... 30
V. Fractional doses
  - Immunology..........................................................................................................................32
  - Feasibility.............................................................................................................................32

VI. Research needs on immunization against meningococcal disease.................................34

VII. Recommendations..................................................................................................................36

VIII. References............................................................................................................................38
I. Background on the disease, routes of transmission, treatment and risk factor

*Neisseria meningitidis* is one of the leading causes of bacterial meningitis globally. It is a gram negative diplococcus that causes disease only in humans. Strains that cause invasive meningococcal disease (IMD) are classified into serogroups based on the type of polysaccharide capsule expressed, and these virulent strains are different from those that reside harmlessly in the nasopharynx resulting in an asymptomatic carrier state. A number of virulence factors have a role in the pathogenesis of the disease including lipoooligosaccharide and surface adhesive proteins along with the polysaccharide capsule.

Colonization of the upper respiratory mucosal surfaces by *N. meningitidis* is the first step in establishing a human carrier state and a precursor to invasive meningococcal disease. Meningococcal transmission among humans occurs largely through respiratory droplets and salivary secretions. In a small proportion of carriers, meningococci overcome host defenses, penetrate the mucosa, and gain access to the blood stream causing systemic disease including meningitis. A combination of bacterial virulence and host susceptibility factors, may alter the colonization state and ultimately lead to meningococcal disease.(1)

Although 12 meningococcal serogroups have been described (A, B, C, 29E, H, I, K, L, Y, W-135, X and Z), the majority of disease is caused by organisms expressing one of six capsule types namely A, B, C, X, Y and W-135.(2) Serogroup W-135 is responsible for recent worldwide outbreaks associated with pilgrims returning from the Hajj. An increase in the incidence of disease due to serotype X has been reported in Africa. Capsule switching between serogroups has reportedly arisen in several geographic areas through *in vivo* recombination during co-carriage, and further evolution and adaptation occurs through import of DNA from other commensal pathogens and phages. (3, 4)

Pathophysiology

The first step in the disease process is attachment of the organism through pili to non-ciliated columnar epithelial cells of the nasopharynx. These pili are classified as ‘major adhesins’ and are expressed in abundance on the bacterial surface. These surface structures have the ability to undergo structural/antigenic variation through import of DNA in order to evade immune detection. This phenomenon occurs frequently in *N. meningitidis* as it is naturally competent to readily take up DNA from the microorganisms in its environment.
Following attachment, meningococci proliferate on the surface of endothelial cells and form small micro-colonies. Close adherence of the organism (mediated by bacterial surface opacity proteins Opa/Opc) to host cells results in recruitment of additional factors with extension of pseudopods that internalize the meningococci (Figure 1). Meningococci are able to replicate inside epithelial cells as they can utilize intracellular iron. The organisms may then transcytose further into the tissues and enter the bloodstream. Translocation across the blood-meningeal barrier, proliferation in the central nervous system (CNS) and meningitis may also occur. However, detectable bacteremia is not required for meningitis to develop, although the vasculature is considered the primary route to the brain. (1)

Once access to the bloodstream is acquired, multiplication of the organism is rapid. In the blood, meningococci produce a strong inflammatory response with activation of the complement and coagulation cascades. A key inducer of cellular inflammatory responses, Lipo-oligosaccharide (LOS), is essential in causing meningococcal sepsis. LOS-induced secretion of various cytokines (e.g., IL-6 and TNF-α), as well as chemokines, ROS (reactive oxygen species) and NO (nitric oxide), leads to endothelial damage and capillary leakage, with necrosis of peripheral tissues and multiple organ failure (Figure 2). LOS levels correlate with mortality rates seen in meningococcal disease.
Resistance to complement-mediated lysis and opsonic and non-opsonic phagocytosis is determined by the expression of the capsule and LPS. This enhances survival both in the blood and the CNS and thus isolates from the blood or CSF are invariably capsulate. Meningococci also have the means to interact with several regulators of the complement pathways which could lead to increased bacterial survival(5).

In summary, the key components in meningococcal survival in the blood are the capsule and LOS. Proteinaceous adhesins play important roles in entry to and exit from the vasculature and may also modulate immune responses.

**Routes of transmission:**

Classically, _N. meningitidis_ was known to spread from human to human through droplets or direct physical contact such as intimate kissing. Most cases arise following transmission from an asymptomatic carrier; nasopharyngeal carriage rates of between 10 and 35% have been reported in healthy adults. However cases have been reported which indicate that the nasopharynx is not the only primary site of infection. The pathogen has been isolated from atypical sites such as the mucous membranes of endocervix, conjunctiva, urethra and anus, implicating orogenital sex and vertical transmission as other possible modes of transmission.(6-9)

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**Fig. 2: Meningococcal penetration of the blood-brain barrier and meninges, leading to meningitis. Source: D. J. Hill and others (2010)**
Signs and Symptoms

Meningococcal disease usually occurs 1–4 days after acquisition of the pathogen but can occur up to 14 days after colonisation. Signs and symptoms of meningococcal disease in infants and young children include fever, poor feeding, irritability, lethargy, nausea, vomiting, diarrhea, photophobia and convulsions. The most characteristic feature of meningococcal septicemia is a hemorrhagic (i.e. petechial or purpuric) rash that does not blanch under pressure. Additional signs in children and adults include neck rigidity, myalgia, swollen joints, mental status changes and ataxia.

Invasive disease can also result in localized infection in other sites including arthritis, myocarditis, pericarditis and endophthalmitis.

Risk factors

Known risk factors for invasive meningococcal disease include smoking or environmental tobacco smoke, crowding, asplenia, HIV infection and travel to epidemic areas. (10) Host genetic factors that predispose to infection include deficiencies in terminal complement components and mannose binding lectin. Other host genetic factors that modify susceptibility and outcome are being discovered, such as polymorphisms in SERPINE1 (plasminogen activator inhibitor) and Surfactant Protein A and D, which influence vulnerability and mortality. (11-14)

Meningococcal disease can affect persons of all ages, but higher rates of invasive disease in developed countries are seen in infants and children less than 4 years of age, adolescents, military recruits, and groups where crowding and new exposures occur such as college students living in dormitories(15). Factors that influence the spread and severity of meningococcal disease include smoking, low humidity, dust and respiratory co-infections.(16, 17) These factors may damage the integrity of the nasopharyngeal mucosa. Sub-Saharan outbreaks coinciding with the dry season highlight the potential role of humidity in damaging the mucosa and producing irritant coughing that aids transmission. In countries with a temperate climate, susceptibility to meningococcal disease is highest in the winter when absolute humidity is low(18, 19).

Diagnosis

The gold standard of diagnosis is isolation of N. meningitidis from sterile body fluid (blood or CSF) or purpural lesion scraping. Since N. meningitidis can be a component of normal nasopharyngeal flora, isolation from this site is not helpful diagnostically. Diagnosis relies on culturing the organism on a chocolate agar plate. However, after parenteral antibiotics are started the isolation rate of meningococci from blood cultures drops from 50% to less than 5% and the likelihhood of CSF being positive by culture or microscopy are also reduced. In these situations, PCR, when available, can complement standard laboratory procedures and confirm the diagnosis as its sensitivity is not affected by therapy initiation.(20) Further testing to differentiate the species includes testing for oxidase (all clinically relevant Neisseria show a positive reaction) and the carbohydrates maltose, sucrose, and glucose test in which N. meningitidis will oxidize the glucose and maltose. Where laboratory facilities are limited and rapid diagnosis is essential,
the latex agglutination test may be used. Although less sensitive than PCR it has a high specificity along with ease of performance. (21)

Prevention

 Clearance antibiotics: Close contacts of a patient with IMD are at increased risk for secondary disease; the attack rate amongst household contacts is 500 to 800 times higher than the general population. Clearance antibiotics are effective in protecting close contacts, and should be started ideally within 24 hours of identification of the index case. Close contacts would include household contacts, child care and preschool contacts and others with direct, prolonged contact with IMD patient secretions. Effective clearance antibiotics including rifampin, ciprofloxacin, ceftriaxone or azithromycin should ideally be started within 24 hours of identification of the index case. Although resistance to these drugs has been identified, most strains of *N. meningitidis* remain sensitive. (22-26)

Rifampin is the drug of choice for children; however a single IM dose of ceftriaxone is as effective as rifampin in eradication of serogroup A, while also has the added advantage of being administered as a single does and is safe in pregnancy. Rifampin is contraindicated during pregnancy.

Vaccination: Capsule based vaccines against several serogroups have been available for over 20 years. However, although purified capsular antigens elicit protective antibody responses, they do not induce long-term memory, are less effective in young children who are at the highest risk of disease, and do not induce sustained herd immunity. To overcome this deficiency, conjugate vaccines have been introduced. Strain specificity is based on the meningococcal capsule or protein vaccines based on meningococcal outer membrane vesicles (Serogroup B).

Vaccination during an outbreak:

When an outbreak is caused by a serogroup against which an effective vaccine exists, polysaccharide and conjugate vaccines have both been used effectively for outbreak control. In some countries, it is routine to offer the vaccine to all close contacts of the patient to prevent late secondary cases not prevented by clearance antibiotics. (27)

Vaccination for routine use:

Conjugated meningococcal vaccines are used in several developed countries for routine use. The countries that have seen the largest impact have implemented both mass catch-up campaigns in broad age groups and added meningococcal vaccines against locally prevalent serogroups in their infant immunization programs. Other countries only use this vaccine in adolescents and people with high risk of meningococcal disease (military recruits, travelers to areas where meningococcal disease is hyperendemic or epidemic, microbiologists who are routinely exposed to isolates of *N. meningitidis*, patients with anatomic or functional asplenia, and patients with terminal complement deficiency). (28-31)
Treatment

Septicaemic shock and raised intracranial pressure in severe meningitis cases are particular concerns in the management of suspected cases of meningococcal disease. (32, 33) Short course long-acting chloramphenicol is used for the treatment of epidemic meningococcal meningitis in sub-Saharan Africa. A randomized non-inferiority trial in Niger showed that ceftriaxone provides an alternative treatment for epidemic meningococcal meningitis due to its efficacy, ease of use, and low cost. Cefotaxime and ceftriaxone show a high degree of in vitro activity against moderately penicillin-susceptible meningococci. (34, 35) Empiric therapy with cefotaxime or ceftriaxone should be started while confirmation of diagnosis is sought. Once the diagnosis is confirmed the treatment can be changed to IV Penicillin G (250000-300000 U/kg/day, divided every 4-6 hours). Alternatively, Ceftriaxone may be used for the entire duration of therapy owing to its easy dosing and reports of development of varying degrees of resistance to Penicillin in several countries. (36-38)

Epidemiological data is critical to tracking the spread of less susceptible strains of N meningitidis and to providing guidance in the empirical selection of antimicrobial agents for treatment. Isolates with decreased susceptibility to penicillin have been identified sporadically from several regions of the United States and widely from Spain, Italy, Turkey and parts of Africa. (36-40) Resistant meningococcal isolates for which the minimum inhibitory concentration to penicillin is more than 1 µg/mL are rare. Most reported isolates are moderately susceptible, with a minimum inhibitory concentration to penicillin of between 0.12 µg/mL and 1.0 µg/mL. Treatment with high-dose penicillin is effective against moderately susceptible strains. (41) In Australia, the percentage of isolates susceptible to penicillin had dropped from a high of 45% to 26% by 2000. (42) In certain developing countries like Vietnam where penicillin resistance is high, IM Chloramphenicol is the standard treatment for Neisseria Meningitidis, but emerging resistance against this drug is a cause for concern. (43) In Africa, a gene study conducted in CDC’s Epidemic Investigation laboratories on 33 serogroup A isolates, collected from 9 countries from 1963-1998 showed full sensitivity to both Chloramphenicol and penicillin. In addition to supportive measures such as fluid resuscitation, inotropic and ventilator support may be used where required. Isolation and droplet precautions of the hospitalized patient are necessary until 24 hours after initiation of effective antibacterial therapy. Detailed guideline for diagnosing and managing meningitis have recently been published (44).

Rifampin and ciprofloxacin are the main antibiotics used for chemoprophylaxis. Resistance to ciprofloxacin it is rare, however, in 2007 and 2008, the first ciprofloxacin-resistant strains of N meningitidis-causing disease were detected in certain areas of the United States. Low level resistance (MICs 0.12–0.25mg/L) exists in Australia, France, Spain and Argentina, Hong Kong and China. (45) Fluoroquinolone resistance is also increasing in India, however the study here found 100% susceptibility to penicillin, azithromycin, ceftriaxone and chloramphenicol. (46) Resistance to rifampin, is also rare. One report from USA had 2 isolates which were resistant. (47) Other such case reports exist but are very few.
II. Epidemiology

Definition of epidemics and endemic situations:
The African meningitis belt originally characterized by Lapeysonnie in 1963 and modified in 1987, is a region in Sub-Saharan Africa, which stretches from Senegal in the west to Ethiopia in the east. (48, 49) This region has the highest incidence of meningococcal disease in the world and frequent epidemics constitute a major public health burden. Case fatality rates of meningitis in the meningitis belt range from 10-50%, and 10-20% of the survivors suffer permanent brain damage(50). The meningitis belt region consists of 300 million people and is characterized by particular climatic features and social habits. The dry season from December to June, is characterized by dry winds and cold nights, and is the period with the highest incidence of epidemics. The WHO definition of a meningococcal disease epidemic used in this paper, specifically for the meningitis belt, is >100 cases/100,000 population/year.

Other countries have not experienced epidemics at the level seen in the African meningitis belt. These countries may be classified according to the level of endemic disease present as high, moderate, low endemicity (Figure 3). This classification does not derive from any standardized definitions; rather it is based on country-specific epidemiological data. It may be used as a guide to direct prevention/immunization efforts by identifying regions that would benefit the most from induction of herd protection and where a vaccine intervention would be most cost-effective.

![Fig. 3: Grouping countries according to IMD attack rates for best allocation of resources](image)

- Epidemic is defined as >100 cases/100,000 population within a large region or the entire country
• High endemic rate is defined as >10 cases/100,000 population per year in a country or large region.
• Moderate endemic rate is defined as 2-10 cases/100,000 population per year in a country or large region.
• Low endemic rate is defined as <2 case/100,000 population per year in a country or large region.

There is no global standardised definition of IMD outbreak outside the meningitis belt. For the purpose of this paper and its affiliated recommendations, we define outbreak as an increase in IMD cases in a defined population above what is expected by place and time.(51)

**Epidemiology of invasive meningococcal disease at country level**

Data on incidence of meningococcal disease is presented below in Tables 1-3. Countries are grouped into priority regions according to the definitions above, using national and published data from the last 20 years. Countries not listed in the table have insufficient published data available regarding epidemiology of IMD and the priority would be for establishing surveillance in these countries.

Table 1. Countries with high endemic rates and/or >=1 epidemic over the last 20 years

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Incidence/100,000 population</th>
<th>Predominant strain</th>
<th>Source</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>European Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td>1999-2008</td>
<td>3.5-14.33</td>
<td>B</td>
<td>(52-54)</td>
<td></td>
</tr>
<tr>
<td><strong>African Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Centrafrique</td>
<td>2004-2009</td>
<td>2.6-12.9</td>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mali</td>
<td></td>
<td>3.3-19.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niger</td>
<td></td>
<td>7.8-90.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nigeria</td>
<td></td>
<td>0.7-52.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RD Congo</td>
<td></td>
<td>7.3-23.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chad</td>
<td></td>
<td>9.6-15.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Togo</td>
<td></td>
<td>6-13.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ghana</td>
<td></td>
<td>0-108</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gambia</td>
<td></td>
<td>4-165</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benin</td>
<td></td>
<td>6-57</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ethiopia</td>
<td></td>
<td>0-104</td>
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(51)
<table>
<thead>
<tr>
<th>Country</th>
<th>Year(s)</th>
<th>Cases</th>
<th>Incidence/Outbreak</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Cameroon</td>
<td>1980-1999</td>
<td>1-224</td>
<td>100,000</td>
<td>(59)</td>
</tr>
<tr>
<td>Guinea</td>
<td></td>
<td>0-17</td>
<td>Epidemic in 2008</td>
<td>(55)</td>
</tr>
<tr>
<td>Cote de Ivoire</td>
<td></td>
<td>0-6</td>
<td>Epidemic in 2006, 2008</td>
<td>(60)</td>
</tr>
<tr>
<td>Kenya</td>
<td>1990</td>
<td>267</td>
<td>X in large outbreaks</td>
<td>(61)</td>
</tr>
<tr>
<td>Guinea Bissau</td>
<td></td>
<td>0-133</td>
<td>Epidemic in 1999</td>
<td></td>
</tr>
<tr>
<td>Burundi</td>
<td>Upto 1999</td>
<td>0-14</td>
<td>Epidemic in 1991-92, 96</td>
<td>(57)</td>
</tr>
<tr>
<td>Mauritania</td>
<td>1980-1999</td>
<td>0-14</td>
<td>A</td>
<td>(57)</td>
</tr>
<tr>
<td>Senegal</td>
<td></td>
<td>0-53</td>
<td>Incidence &gt;50 in 1983</td>
<td></td>
</tr>
<tr>
<td>Rwanda</td>
<td></td>
<td>0-28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanzania</td>
<td></td>
<td>0-19</td>
<td></td>
<td></td>
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<tr>
<td>Namibia</td>
<td></td>
<td>4-165</td>
<td>Epidemic in 1994</td>
<td></td>
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<tr>
<td>Uganda</td>
<td></td>
<td>0-18</td>
<td>Epidemic in 2006-07</td>
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<td><strong>Eastern Mediterranean Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sudan</td>
<td>*</td>
<td>A</td>
<td>Epidemic in 2006, 2008</td>
<td>(55)</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>A, W-135</td>
<td>225 cases in month after 2000 Hajj season</td>
<td>(63)</td>
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<tr>
<td><strong>Region of the Americas</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Uruguay</td>
<td>2001</td>
<td>30(pre-vaccine)</td>
<td>B</td>
<td>(64)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.6(post-vaccine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Western Pacific Region</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>New Zealand</td>
<td>1991-2000</td>
<td>17.4(pre-vaccine)</td>
<td>B</td>
<td>(65)</td>
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<tr>
<td></td>
<td></td>
<td>2.6(post-vaccine)</td>
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* Data not available
Table 2. Countries with moderate endemic rates

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Incidence/100,000 population</th>
<th>Predominant strain</th>
<th>Source</th>
<th>Comments</th>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Malta</td>
<td>1994-2007</td>
<td>0.8-8.9</td>
<td>B, C</td>
<td>(66)</td>
<td>2 peaks in 2000 and 2006</td>
</tr>
<tr>
<td>Belgium</td>
<td>1990-2008</td>
<td>3.69 (pre-vaccine) 0.8 (post-vaccine)</td>
<td>B, C</td>
<td>(67)</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>1999-2006</td>
<td>3.74(pre-vaccine) 1.3(post-vaccine)</td>
<td>B, C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iceland</td>
<td>1999-2006</td>
<td>7.58(pre-vaccine) 1.3(post-vaccine)</td>
<td>B, C</td>
<td>(67)</td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td>1999-2008</td>
<td>1.2-3.5</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luxemburg</td>
<td>1999-2008</td>
<td>0-4.15</td>
<td>*</td>
<td>(52)</td>
<td></td>
</tr>
<tr>
<td>Greece</td>
<td>1999-2008</td>
<td>0.65-2.39</td>
<td>C</td>
<td></td>
<td>A conjugate vaccine for group C introduced in 2001 in pediatric population, dramatic drop in C cases by 2004 (68)</td>
</tr>
<tr>
<td>Netherlands</td>
<td>1999-2008</td>
<td>4.51(pre-vaccine) 1.1(post-vaccine)</td>
<td>B, C</td>
<td>(54, 69)</td>
<td></td>
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<tr>
<td>Switzerland</td>
<td>1992-2008</td>
<td>1.02-2.43</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td>1992-2008</td>
<td>0.74-4.6</td>
<td>B</td>
<td>(70)</td>
<td></td>
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<tr>
<td>Portugal</td>
<td>2000-08</td>
<td>0.55-2.08</td>
<td>B, C</td>
<td></td>
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<tr>
<td>Turkey</td>
<td>1997-2006</td>
<td>0.3-2.2</td>
<td>*</td>
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<tr>
<td>Lithuania</td>
<td>1997-2007</td>
<td>1.7-2.7</td>
<td>*</td>
<td>(54)</td>
<td></td>
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<tr>
<td>United Kingdom</td>
<td>1999-2008</td>
<td>5.39(pre-vaccine) 2.1(post-vaccine)</td>
<td>B, C</td>
<td>(54)</td>
<td></td>
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<td><strong>African Region</strong></td>
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<td></td>
<td></td>
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<tr>
<td>South Africa</td>
<td>2000-05</td>
<td>0.8-4</td>
<td>B in Western Cape</td>
<td>(71)</td>
<td>High rates in 2005 from one province. W-135 endemic, emerging &amp; more severe than A in northern Provinces</td>
</tr>
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<td><strong>Region of the Americas</strong></td>
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<td></td>
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<tr>
<td>Cuba</td>
<td>1998-2003</td>
<td>3.4-8.5(pre-vaccine) &lt;1(post-vaccine)</td>
<td>B</td>
<td>(72)</td>
<td></td>
</tr>
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<td>Argentina</td>
<td>1998-2006</td>
<td>0.7-2.4</td>
<td>B</td>
<td>(64)</td>
<td>Pediatric population</td>
</tr>
<tr>
<td>Brazil</td>
<td>1998-2006</td>
<td>1-4.5</td>
<td>B, now C</td>
<td>(64)</td>
<td>Epidemics in 1970s, peak incidence 179</td>
</tr>
<tr>
<td><strong>Western Pacific Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>1995-2006</td>
<td>3.5-7.9(pre-vaccine) 1.4(post-vaccine)</td>
<td>B</td>
<td>(73)</td>
<td></td>
</tr>
</tbody>
</table>

* Data not available
### Table 3. Countries with low endemic rates

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Incidence/100,000 population</th>
<th>Predominant strain</th>
<th>Source</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>European Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td></td>
<td>0.74-1.32</td>
<td>B, C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulgaria</td>
<td></td>
<td>0.26-0.51</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyprus</td>
<td></td>
<td>0.25-0.51</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Czech Republic</td>
<td></td>
<td>0.73-1.2</td>
<td>B, C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estonia</td>
<td></td>
<td>0.44-0.96</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td></td>
<td>0-1.11</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>1999-2008</td>
<td>0.74-1.31</td>
<td>B, C</td>
<td>(52)</td>
<td>Rate 6.9-9.4/100,000 in ages 1-18 (74)</td>
</tr>
<tr>
<td>Italy</td>
<td></td>
<td>0.25-0.56</td>
<td>B, C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slovenia</td>
<td></td>
<td>0.3-1.2</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td></td>
<td>0.37-0.65</td>
<td>B, C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td></td>
<td>0.09-0.88</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td>0.49-0.7</td>
<td>B, C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hungary</td>
<td></td>
<td>0.3-0.43</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latvia</td>
<td>2003-08</td>
<td>0.26-1.03</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slovakia</td>
<td></td>
<td>0.59-0.91</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serbia</td>
<td>2000</td>
<td>0.9</td>
<td>*</td>
<td>(54)</td>
<td></td>
</tr>
<tr>
<td>Albania</td>
<td>1999</td>
<td>0.8</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croatia</td>
<td>1997-2006</td>
<td>0.7-1.3</td>
<td>*</td>
<td></td>
<td>Rates rising</td>
</tr>
<tr>
<td><strong>African Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mauritius</td>
<td>2001-02</td>
<td>*</td>
<td>W-135 (Haj)</td>
<td>(75)</td>
<td>4 cases in this year</td>
</tr>
<tr>
<td><strong>Region of the Americas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>2000-09</td>
<td>0.8(pre-vaccine)</td>
<td>Equal B, C, Y</td>
<td>(76)</td>
<td>Routine vaccination program started in 2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.28(post-vaccine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>1985-2006</td>
<td>1.38(pre-vaccine)</td>
<td>C</td>
<td>(77, 78)</td>
<td>Vaccination in 2001-2 in all provinces</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.42(post-vaccine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td>1998-2006</td>
<td>0.06</td>
<td>C</td>
<td>(64)</td>
<td></td>
</tr>
<tr>
<td>Venezuela</td>
<td></td>
<td>0.3</td>
<td>Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Columbia</td>
<td></td>
<td>0.3</td>
<td>Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chile</td>
<td></td>
<td>0.8</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Western Pacific Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>1974-2003</td>
<td>*</td>
<td>B</td>
<td>(79)</td>
<td>182 cases in these 30 years</td>
</tr>
<tr>
<td>Malaysia</td>
<td>1987-2004</td>
<td>*</td>
<td>*</td>
<td>(80)</td>
<td>12 cases from 1 hospital in Kuala Lumpur</td>
</tr>
<tr>
<td>China</td>
<td>2000 onwards</td>
<td>&lt;0.2</td>
<td>A, C</td>
<td>(81, 82)</td>
<td>Epidemics in 1960s, 70s and 80s with serogroup A,</td>
</tr>
<tr>
<td>Region</td>
<td>Year</td>
<td>Group</td>
<td>Rate</td>
<td>Cases/Year</td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------</td>
<td>-------</td>
<td>------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td><strong>South East Asia Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thailand</td>
<td>1994-99</td>
<td>*</td>
<td>36</td>
<td>36 cases from 13 govt. hospitals in 5 years</td>
<td></td>
</tr>
<tr>
<td>Korea</td>
<td>2002-03</td>
<td>Y</td>
<td>11</td>
<td>cases in this year</td>
<td></td>
</tr>
</tbody>
</table>

| **Eastern Mediterranean Region** |        |       |      |            |
| Egypt                    | 1990-96| A,B   | (85) | 3000 cases in 1990 down to 670 in 1996, vaccine introduced in 1992 |
| Iran                     |        | *     |      | 150 to 500 cases per year |
| Iraq                     |        | *     |      | 3000-5000 cases per year |
| Jordan                   |        | *     | 30-60 cases per year |
| Kuwait                   |        | *     | 5-10 cases per year |
| Morocco                  |        | *     |      | 200-800 cases per year |
| Oman                     |        | *     | 10-30 cases per year |
| Pakistan                 | 1990-96| *     | (86) | 5000-6000 cases per year |
| Qatar                    |        | *     |      | 0-1 case per year |
| Syria                    |        | *     |      | 200-500 cases per year |
| Tunisia                  |        | *     |      | 300-450 cases per year |
| UAE                      |        | *     |      | 40-70 cases per year |
| Yemen                    |        | *     |      | 400-600 cases per year |

*Rates not available
**Serogroups/Serotypes**

*N. meningitidis* is classified into 13 serogroups based on the immunogenicity and structure of the polysaccharide capsule. Further classification into serosubtype, serotype and immunotype is based on class 1 outer membrane proteins (PorA), class 2 or 3 (PorB) outer membrane proteins and lipopoly[oligo]saccharide structure, respectively. (1) Figure 4 below shows commonly found and predominant serogroups in different regions of the world.

![Figure 4: Distribution of common and predominant meningococcal sero-groups by region. Predominant strains are highlighted in bold text.](image)

**Carriage**

Strains of Neisseria commonly reside in the human nasopharynx asymptomatically. Studies put carriage rates in healthy adults at between 10 and 35% depending on populations sampled, and sampling sites and techniques. (87, 88) Higher carriage rates have been found in some confined populations like university students and army recruits.(89-91). (92)

Although carriage is a necessary step for the development of invasive disease, the transition from carriage to invasive disease is rare owing to differences in the genetic composition and capsule
structure of pathogenic and non-pathogenic strains (even within the same serogroup) as well as host susceptibility factors. Isolates from carriers may be capsulated or may not have a capsule, whereas blood and CSF isolates invariably have a capsule. Moreover, 10-14 days post acquisition of the pathogen, invasive disease becomes highly unlikely. This can be related to the appearance in serum of antibodies against the bacteria within two weeks after nasopharyngeal colonization. (1, 2, 93) Carriage studies may be helpful in understanding transmission dynamics but are not useful to predict the course of an epidemic.

Outbreaks following the Hajj (muslim pilgrimage to Mecca, Saudi Arabia) in 1987 and 2001 are good examples of widespread transmission of *N. meningitidis* leading to disease outbreaks in multiple countries. (94, 95) In 1987, there was an outbreak with serogroup A, and in 2001 serogroup W-135 was shown to be the causative agent of meningococcal epidemic in several countries following Hajj. A number of carriage studies were conducted on returning pilgrims in 2001 to assess the risk to close contacts. A study in Singapore on returning pilgrims estimated 15% of them to be carrying W135 and 55% of them to still be carriers 6 months later. These people transmitted the pathogen to 8% of their unvaccinated household contacts within the first few weeks of return, but no late transmissions were reported. Other countries showed significantly lower carriage among travelers and lower risk among household contacts. This pathogen was carried back to regions as far apart as China and Latin America, and is now the third most predominant serogroup in Brazil and Argentina. Serogroup W-135 caused an epidemic in Burkina Faso in 2002. Studies done in the region showed that the subtype of W-135 (ST-11) was identical to the one isolated during the Hajj epidemic; however, very closely related strains had been found in multiple countries including previously Africa. (96-99)

**Duration of protection against natural disease/acquisition of natural immunity**

In the neonate, immunity to systemic meningococcal infection is associated with the passive transfer of IgG antibodies from mother to fetus, although transplacental transport of antibodies is suboptimal in preterm infants. (100, 101) Many studies have been conducted to evaluate the best measure of immunity after carriage or vaccination. Current expert consensus suggests that hallmark of immunity to meningococcal disease is a Serum Bactericidal Antibody (SBA) activity which is a measure of antibody-mediated, complement-dependent killing. (99) A cardinal study by Goldshneider et al in 1970 showed that the bactericidal activity that develops in response to carriage is not limited to the strain that is being carried, but can also extend to heterologous strains of pathogenic meningococci (groups A, B, C) and subsequent development of specific IgG, IgM and IgA. (102-104) This response may last several months after the carried strains can no longer be detected. However, it is not clear whether natural immunization leads to immunological memory. Also, although specific immunity is generally protective, this immunity is not absolute; meningococcemia can occur in individuals with preexisting antibody titers that are considered protective. (105)
Age-specific attack rates

In most countries with epidemiological the age distribution of meningococcal disease demonstrates two peaks. The highest incidence is in infants less than one year of age, and a secondary rise in incidence occurs in adolescents and young adults. Fifteen years of data from Niger shows that under-5 year olds were more affected during epidemics when compared to non-epidemic years. However, some studies have suggested a shift towards older age groups during epidemics. Figures 5-8 below depict age specific attack rates for selected countries. Figure 10 shows the correlation between the peak in infancy and low serum bactericidal antibody titers and increasing titers in adulthood with decreasing incidence of disease.

![Graph showing age-specific incidence rates](image)

**Fig.5: Age specific incidence in the United States from 2000-2009. Source: Active Bacterial Core Surveillance**

Figure 7. Age specific incidence and case-fatality ratio of laboratory confirmed meningococcal infection, Europe, 2006. Source: European Union Invasive Bacterial Infections Surveillance Network (EU-IBIS)
Figure 8. Proportion of meningitis cases due to specific organisms during 11 inter-epidemic years in Niamey, Niger. (1981-1994) (106)

Fig. 9: Changing epidemiology of pyogenic meningitis in India. (108)
Fig. 10: Relationship of incidence of disease and Serum Bactericidal Antibodies with age for serogroup B (108)

Use of vaccines

Currently available meningococcal vaccines include both polysaccharide vaccines and polysaccharide-protein conjugate vaccines based on the meningococcal capsule. For serogroup B, development has included protein vaccines based on meningococcal outer membrane vesicles; more recently a range of conserved proteins including fHBP and nAdA have been used as vaccine components.

Table 4. Comparison of the immune response to polysaccharide and conjugate vaccines.(109)

<table>
<thead>
<tr>
<th></th>
<th>Polysaccharide</th>
<th>Conjugate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunogenicity</td>
<td>Adults</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Young children</td>
<td>Poor</td>
</tr>
<tr>
<td>Quality of antibodies</td>
<td>Avidity</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Bactericidal activity</td>
<td>Low</td>
</tr>
<tr>
<td>Response to booster</td>
<td>Poor</td>
<td>High</td>
</tr>
<tr>
<td>Induction of immunologic memory</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>Reduction of colonisation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Duration of Protection</td>
<td>Short</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Polysaccharide vaccines have high serogroup specificity, but show poor immunogenicity in infancy (except for MenA) (Table 4). Hypo-responsiveness (as defined by impaired serum anticapsular antibody responses to subsequent injections of vaccine after the initial dose) to Men C polysaccharide in infancy has been shown, especially if doses are repeated more than once. There is also an age dependent decline in antibody levels after vaccination. (110-113)

Polysaccharide and conjugate vaccines for serogroup A, C, W135 and Y are already available for purchase. Strain-specific serogroup B outer membrane vesicle vaccines are licensed and used in several countries but are not widely available.

Conjugate vaccines have had a profound effect on incidence of meningococcal disease in countries where they have been introduced by mass campaigns followed by routine infant immunization, even benefitting unvaccinated individuals through the induction of herd protection. Table 5 lists these countries and their current immunization schedules for meningococcal vaccines.

**Table 5.** Countries that have introduced meningococcal vaccines in using mass immunization and/or routine immunization programs

<table>
<thead>
<tr>
<th>Country</th>
<th>Source</th>
<th>Vaccine</th>
<th>Year introduced</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa (Burkina Faso, Niger, Mali)</td>
<td>MVP</td>
<td>MenAfriVac™</td>
<td>2010</td>
<td>Mass vaccination of 1-29 year old with a single dose</td>
</tr>
<tr>
<td>Canada</td>
<td>NACI</td>
<td>MenC conjugate Menactra approved in 2006,</td>
<td>2002</td>
<td>Most provinces use the MenC conjugate at 12 months while a few use the quadrivalent conjugate based on local epidemiology and/or children &gt;2 years with primary antibody deficiencies</td>
</tr>
<tr>
<td>China</td>
<td>(82)</td>
<td>MenA polysaccharide MenA/C polysaccharide</td>
<td>1982, 2005</td>
<td>Vaccine at 6 and 18 months Used as booster at 3 and 6 years</td>
</tr>
<tr>
<td>Cuba</td>
<td>(115)</td>
<td>VA-MENGO-BC</td>
<td>1991</td>
<td>Introduced into National Infant Immunization Program after epidemic incidence levels in 1980s</td>
</tr>
<tr>
<td>Egypt</td>
<td>(85)</td>
<td>A/C Polysaccharide</td>
<td>1992</td>
<td>School based vaccination program</td>
</tr>
<tr>
<td>Iceland</td>
<td>(116)</td>
<td>MenC conjugate</td>
<td>2002</td>
<td>6 and 8 months of age Up to 19 years</td>
</tr>
<tr>
<td>Netherlands</td>
<td>(69, 117)</td>
<td>MenC conjugate</td>
<td>2002-3</td>
<td>Single dose at 12 or 14 months Up to 18 years of age (to 1 year in parts of</td>
</tr>
<tr>
<td>Country</td>
<td>Vaccine Type</td>
<td>Year</td>
<td>Ages in Schedule</td>
<td>Age Limit</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------------</td>
<td>-------</td>
<td>-----------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Belgium</td>
<td>MeNZB MenC conjugate</td>
<td>2004</td>
<td>Mass immunization for everyone aged between 6 months and 20 years. MeNZB routine use has now been terminated due to a marked decrease in the incidence of meningococcal B disease</td>
<td>Belgium offered to all young adults</td>
</tr>
<tr>
<td>Australia</td>
<td>IMAC MenC conjugate</td>
<td>2004</td>
<td>Mass immunization for everyone aged between 6 months and 20 years. MeNZB routine use has now been terminated due to a marked decrease in the incidence of meningococcal B disease</td>
<td>Belgium offered to all young adults</td>
</tr>
<tr>
<td>New Zealand</td>
<td>IMAC MenC conjugate</td>
<td>2004</td>
<td>Mass immunization for everyone aged between 6 months and 20 years. MeNZB routine use has now been terminated due to a marked decrease in the incidence of meningococcal B disease</td>
<td>Belgium offered to all young adults</td>
</tr>
<tr>
<td>Portugal</td>
<td>MenC conjugate</td>
<td>2001</td>
<td>3, 5 and 15 months of age</td>
<td>Up to 18 years</td>
</tr>
<tr>
<td>Spain, Ireland</td>
<td>MenC conjugate</td>
<td>2000-2001</td>
<td>Part of routine immunization at 2, 4 and 6 months of age (now 4, 6 months and second year of life in Ireland)</td>
<td>Up to 19 years in Spain (most regions), Up to 23 years (Ireland)</td>
</tr>
<tr>
<td>UK</td>
<td>MenC conjugate</td>
<td>1999</td>
<td>Part of primary immunisation schedule at 2, 3 and 4 months of age. From 2006 at 2, 4, 12 months of age</td>
<td>Up to 18 years of age (1999-2000), up to 25 years (2001)</td>
</tr>
<tr>
<td>USA</td>
<td>MCV4 (Menactra)/ Menevo/MPSV4 acceptable alternative</td>
<td>2005</td>
<td>Primary dose at age 11-12 years with a booster dose at age 16, people at increased risk as mentioned above Booster dose at 5 years</td>
<td>Adolescents aged 13-18</td>
</tr>
</tbody>
</table>

In England and Wales, after the introduction of MCC in 1999, the impact on serogroup C disease has been sustained with the lowest recorded incidence (0.02 cases per 100,000 population) in the 2008-2009, although protection (SBA titers) has not been long lasting. (123) This impact on disease epidemiology has been attributed to the development of herd protection due to reduced carriage. Similar results have been shown in Canada (114) and Australia. (124) Induction of long term humoral memory development is another potential advantage of vaccination, although in practice the response has not been as significant as that induced by conjugate vaccines against other diseases. (125, 126) Nonetheless, studies have also shown that antibody responses are higher after booster doses than in vaccine-naïve adults making a case for a multiple dose regimen against N. meningitides. (127, 128)

**Replacement Disease**

*N. meningitidis* has been shown to switch capsules. For example, the ST11/ET37 strain had been identified in both serogroup B and W135. (129, 130) Moreover, meningococci of different serogroups, B and C, but with identical serotype and electrophoretic type were detected in the Czech Republic, Canada, and the Pacific Northwest, which raised the possibility that genetic
exchange between epidemic and endemic strains may be more common than previously suspected. (131-134)

Despite these concerns, current evidence does not show significant replacement disease after the introduction of meningococcal vaccines. Extensive carriage studies and surveillance after introduction of MenC in the UK in 1999 have found no evidence of capsule replacement following mass immunization with MenC conjugate vaccines from 1988-2005 (135). This time period extended from the pre-vaccination era to 5 years after mass vaccination with MenC. The results were supported by studies conducted in other countries, including Spain and Italy, which showed that the presence of the hyper-virulent strains of different serogroups but same electrophoretic subtype was either insignificant post vaccination or occurred even without mass vaccination. (136, 137) A study done in Spain to analyze the possible impact of two vaccination campaigns (with A/C polysaccharide in 1997 and MenC conjugate from 2000-2008) showed that the overall diversity of the meningococcal population, measured by the frequency of STs and clonal complexes, numbers of alleles, polymorphic sites, and index of association, remained relatively constant throughout the study period. (138)
III. Immunology, Safety and Effectiveness of Meningococcal Vaccines

Correlates of protection against meningococcal disease

Due to the relatively low incidence of meningococcal disease, pre-licensure clinical effectiveness studies are not feasible. Meningococcal vaccines are licensed based on evidence of an immune response in subjects receiving vaccine using serum bactericidal activity (SBA) as the immunologic correlate of protection.

Goldschneider et al., demonstrated that SBA levels correlates with protection against serogroup C meningococcal disease using human complement (hSBA). Titers of 1:4 were shown to confer protection against disease. hSBA has since been considered the gold standard correlate of protection (139, 140). As it is difficult to obtaining immunologic naïve samples of human complement, baby rabbit complement is more frequently used in the assays. Because meningococci are more susceptible to lysis by rabbit complement, correlates of protection were re-evaluated to identify serologic titers that could be used as proxies for effective protection. Subsequent studies have shown rSBA titers (serogroup C) of ≥1:8 reliably predicted protection in humans (141-144). While the SBA titers indicating protection were established based on serogroup C disease, they are generally accepted as correlates of protection for other serogroups.

Field effectiveness of vaccines

Post-licensure field effectiveness studies are critical to evaluate the true impact of a vaccination program, and to inform decisions about future vaccination strategies. All of the vaccines discussed below induce strong immunogenic responses (SBA titers) when evaluated one month after vaccination. It is the intersection of the properties of a vaccine, the specific vaccination strategy, program coverage, and disease epidemiology that determine how well a vaccine works in the field. For example, polysaccharide vaccine is highly effective against serogroup C outbreaks in military barracks when given prior to the start of basic training because these outbreaks occur shortly after the start of basic training, vaccination coverage is likely 100%, and antibody titers are still high. However, polysaccharide vaccines are less effective at producing long term control against serogroup A outbreaks in Africa because they are less immunogenic in young children, do not provide long-term protection, and there are no benefits of herd protection. A study done in 1985 to detect age-specific differences in duration of clinical protection after vaccination with MenA polysaccharide vaccine showed that a single dose does not yield lasting protection in children aged less than 4 years. (145)

Duration of immunity

When using meningococcal vaccines to prevent or halt disease outbreaks, short-term protection is sufficient. However, routine vaccination programs against meningococcal disease require vaccines that provide long-term protection or high levels of herd protection in order to reduce disease burden. Meningococcal conjugate vaccines were developed because polysaccharide vaccines had a limited duration of protection, especially in infants and young children. The
ability of conjugate vaccines to induce a T-cell immune response, with benefits including immunologic memory and impact on nasopharyngeal carriage, makes them better vaccines to use for long-term protection against meningococcal disease.

There are three characteristics of conjugate vaccines that are important for establishing long term control against a bacterial pathogen: circulating antibody, a memory response, and herd protection (146). SBA titers decline after vaccination with all meningococcal vaccines, although this is more pronounced in infants and young children and the rate of antibody decline may vary based on the characteristics of each vaccine. However, if the initial response to a vaccine induces higher SBA titers, the antibody titers may be protective for longer even if the rate of declining titers is the same as other vaccines.

Immunologic memory means there are circulating memory cells that can result in a strong and rapid immunologic response to the next antigen exposure (either the pathogen or through vaccination). In one study of 4 year old children, following conjugate vaccination initially at 2, 3 and 4 months of age, rSBA titers increased 1000 fold (GMT levels) and geometric mean avidity index was 1.33 fold higher one month following a booster vaccine dose (147-152).

We do not have enough experience yet to truly understand the duration of protection from OMV and other serogroup B meningococcal vaccines that do not include polysaccharide as an antigen.

**Herd protection**

Herd protection is an important component of long-term community protection against meningococcal disease. MenC conjugate vaccines induced herd protection when used in the UK with reduced nasopharyngeal carriage and decreased transmission to non-vaccinated populations (153). The UK achieved high coverage in children aged 0-18 years very rapidly. A majority of serogroup C disease was caused by a single clone which caused high rates of disease for several years prior to vaccination. Even though antibody titers in a large portion of the population have now declined, there is almost no serogroup C disease in the UK and it appears that the indirect benefits of herd protection are a major contributor to long-term decrease in disease incidence in the UK.

Whether different meningococcal vaccine programs will see the same benefit of herd protection likely depends on the coverage of the program and the vaccination strategy used. In the United States, quadrivalent meningococcal conjugate vaccine was introduced in 2005 and added to the routine schedule only for adolescents aged 11-18 years. Five years after introduction vaccination coverage is only 52% (NIS). While the incidence of disease in the US has decreased in those who have been vaccinated, there is little evidence of wide scale herd protection with this vaccine program. High vaccination coverage in the age group that likely transmits the organism (older adolescents) is a key factor for achieving herd protection. In Netherlands, one dose of conjugate vaccine in the second year of life has significantly reduced the incidence of Men C disease and a similar pattern has been seen in Australia where after an initial campaign included all children and young adults, routine immunization now occurs at 12 months of age (69). It remains to be seen whether MenB vaccines in development will impact nasopharyngeal carriage.
Polysaccharide Meningococcal Vaccines

There are several combinations of polysaccharide vaccines used globally, including bivalent (A,C), trivalent (A,C,W-135) and quadrivalent (A,C, Y, W-135) vaccines. The first polysaccharide vaccines were developed at Walter Reed Army Institute and implemented in military recruits to prevent recurrent outbreaks among young soldiers (140, 154). Polysaccharide meningococcal vaccines are immunogenic and safe. They are highly effective in closed populations of adults at high risk for disease including military recruits and household contacts of affected individuals (155-157) and in outbreak control.(158) Serogroup A vaccine has also been used effectively during outbreaks in Africa (159-161).

Although a few countries had a routine vaccination program with polysaccharide vaccines prior to conjugate vaccines (Syria, Saudi Arabia), they have been used typically to protect persons at increased risk for disease, e.g. following splenectomy or travellers to the Hajj, or in reactive vaccination campaigns in response to outbreaks in developed countries and especially in the African Meningitis Belt.

Conjugate meningococcal vaccines

Meningococcal conjugate vaccines were introduced in 1999 with initial introduction of MenC conjugate vaccines in the UK. Since then, quadrivalent (A,C,Y,W-135) and monovalent MenA vaccines have been licensed in certain countries (Table 6). Multiple countries have since introduced conjugate vaccines into their routine vaccination schedules. Conjugate vaccines use a carrier protein to present the polysaccharide antigen to the immune system, inducing a T-cell immune response. Ten years of experience in countries with adequate surveillance systems have shown conjugate vaccines to be safe and effective, with large reductions in meningococcal disease burden as a result of vaccine introduction in countries with adequate surveillance systems. However, questions remain regarding long-term effectiveness of conjugate vaccines and how to optimize routine vaccination programs.

Table 6. Meningococcal Conjugate Vaccine Products

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Manufacturer</th>
<th>Serogroups</th>
<th>Protein Conjugate</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menveo™</td>
<td>Novartis Vaccines</td>
<td>A, C, Y, W-135</td>
<td>Diphtheria cross reactive material 197 (CRM&lt;sub&gt;197&lt;/sub&gt;)</td>
<td>(162, 163)</td>
</tr>
<tr>
<td>Menactra™</td>
<td>Sanofi Pasteur</td>
<td>A, C, Y, W-135</td>
<td>Diphtheria toxoid</td>
<td>(30, 164, 165)</td>
</tr>
<tr>
<td>Meningitec™</td>
<td>Wyeth Vaccines</td>
<td>C</td>
<td>CRM&lt;sub&gt;197&lt;/sub&gt;</td>
<td>(166)</td>
</tr>
<tr>
<td>Menjugate®</td>
<td>Novartis Vaccines</td>
<td>C</td>
<td>CRM&lt;sub&gt;197&lt;/sub&gt;</td>
<td>(167, 168)</td>
</tr>
<tr>
<td>NeisVac-C™</td>
<td>Baxter Bioscience</td>
<td>C</td>
<td>Tetanus toxoid</td>
<td>(169)</td>
</tr>
<tr>
<td>MenAfriVac™</td>
<td>Serum Institute of India</td>
<td>A</td>
<td>Tetanus toxoid</td>
<td>(170, 171)</td>
</tr>
</tbody>
</table>
MenC conjugate vaccines

Meningococcal C conjugate (MCC) vaccine was first licensed in the UK without pre-licensure Phase III clinical trials. Several vaccine products are now licensed, conjugated to either tetanus toxoid or Crm-197. Multiple studies have since evaluated the safety and immunogenicity of MCC vaccination in several countries. Studies in healthy adults show a significant rise in geometric mean titers (GMT) from under 40 to 700-3000 one month after vaccination (149, 172). Similar results have been seen in healthy adolescents (173). At least five studies found MCC to be safe, with no major adverse reactions and only minor local reactions (150, 174-177). Immunogenicity studies have shown MCC to be immunogenic in infants as well as adults; prior to moving the third dose to 12 months of age in the UK, Borrow, et al. found only 8-12% of children completing a 3 dose series in infancy to have rSBA titers $\geq 1:8$ at 4 years of age, with GMTs similar to pre-vaccination levels (178). In a phase 4 clinical trial of 250 children in the UK, rSBA titers were tested 6 years after the primary MCC series. Age at priming ranged from 2 months to 6 years. Only 25% (CI 20%-30%) of all children had protective titers $\geq 1:8$ (179).

Recent data from the United Kingdom indicate that the memory response may not be rapid enough to protect against meningococcal disease if a booster is provided following close contact. After initial priming with monovalent MenC conjugate vaccine, a memory response after a booster dose is not measurable until 5 to 7 days later. (143) The incubation period of meningococcal disease is usually less than 3 days. Therefore, while a memory response may protect some individuals from disease or ameliorate disease severity, already present circulating antibody may be a more important indicator of direct long-term protection against meningococcal disease.

Antibody responses were similar when MCC was co-administered simultaneously with routine infant immunizations (180-182). Further studies have shown that a two dose series at 3 and 5 months yields equivalent immunity (148, 181, 183).

Quadrivalent meningococcal conjugate vaccines

In 2005, the first quadrivalent meningococcal conjugate vaccine (A,C,W,Y) conjugated to diphtheria toxin was licensed by the US Food and Drug Administration. A second MenACWY vaccine conjugated to Crm-197 was licensed in 2010. In pre-licensure clinical studies, both vaccines were found to be safe and immunogenic. In the United States these vaccines are licensed for ages 2-54 years, with studies evaluating multiple dose series in infants and toddlers having just been completed.

MenA conjugate vaccine

While meningococcal conjugate vaccines have the attributes needed to eliminate epidemic meningitis is Africa, including eliminating carriage of the organism, previous monovalent and quadrivalent meningococcal conjugate vaccines used in developed countries are too costly for widespread and sustainable use in the African Meningitis Belt. The Meningitis Vaccine Project...
was started in 2001 as a collaboration with multiple partners, including WHO and PATH, to bring an affordable conjugate vaccine targeting serogroup A to the African Meningitis Belt.

In 2010, Meningococcal A conjugate vaccine (MenAfriVac), manufactured by the India Serum Institute, was licensed and prequalified by WHO for use. In Sept. 2010, MenAfriVac was introduced in mass vaccine campaigns in Burkina Faso, Mali, and Niger. All persons age 1-29 years were vaccinated in the districts included in the campaigns. This vaccine has been shown to be highly immunogenic and the safety profile is comparable to the safety profile of polysaccharide vaccine (184). One year after vaccination, the proportion of subjects who were responders was the same as the proportion 28 days after vaccination (83%). Infants also have strong responses to a 3 dose primary series with MenAfriVac. The vaccine effectiveness and impact on disease burden these vaccines will have is being monitored closely.

Vaccine effectiveness (VE) varies by conjugate vaccine and how the program was implemented, but is clearly higher in older children and adolescents compared to young children, with studies reporting VE as high as 97% for MenC vaccine in teenagers Short term VE was high (83%) in those receiving immunization but declined with time, particularly in those vaccinated in infancy or pre-school age. Estimates of VE over time in those vaccinated in infancy fell from 95% in the first year to 31% by the fourth year after vaccination. (123, 185-187). In the United States, initial VE estimates of 75% have been found with MenACWY vaccine in adolescents. (162) Analyses of vaccine failures have found evidence of priming but low SBA activity in many of those vaccinated. Aukland, et al. have reported 53 cases of vaccine failure, largely in healthy children who had received a primary vaccination series in infancy. All cases mounted an anamnestic immune response (188).

Another measure of the effectiveness of the meningococcal conjugate vaccination programs is its herd effects. Two years after introduction of MCC vaccine in the UK, the serogroup C carriage rate was reduced by 81% (189). Attack rates among unvaccinated children and adults in the UK declined by 67% in the 4 years following vaccine introduction. Between 1998 and 2009, the incidence of serogroup C disease in persons over 25 years dropped from 0.55 / 100,000 persons to 0.02 / 100,000 persons in the UK; and the number of cases in infants under 3 months of age dropped from 13 in 1998 to 1 in 2009 (123). These effects were seen despite a declining seroprevalence of protective antibodies among vaccination cohorts as early as 18 months after the last scheduled dose of vaccine (190).

Implementation of meningococcal conjugate vaccination programs in countries across Europe, North America and Australia, have all documented a reduction in serogroup C incidence. In the UK, incidence has decreased by 97% since 1998. The number of deaths from serogroup C disease declined from 78 in 1998 to 1 in 2009 (191). In Canada, incidence declined 65% five years after implementation. Ontario saw a 16% reduction per year in serogroup C disease among persons ≥20 years of age from 2000-2006 after introducing a MCC vaccination program in adolescents and infants (114). No such reduction was seen in other serogroups that were not included in the vaccine (78). Dramatic reductions in disease incidence have also been recorded in Australia, Netherlands, Spain, and Greece (68, 69, 192, 193). Since quadrivalent vaccine was introduced in the United States, overall incidence of meningococcal disease has declined by
64.1%. This decline in incidence was seen in infants too young to be vaccinated and persons over 20 years, again indicating possible herd effects (194) although as the decline was also seen in other serogroups, including serogroup B, some of this change may be due to cyclic variation.

**MenB OMV vaccines**

While progress towards reducing meningococcal disease globally has been made with meningococcal conjugate vaccines for serogroups A, C, Y and W-135, vaccines to protect broadly against serogroup B disease have presented a challenge because the B polysaccharide is not immunogenic and other potential antigen targets are highly diverse. Serogroup B vaccines have been developed for specific outbreak strains using the outer membrane vesicles (OMV) specific to that strain, including vaccines to target disease in New Zealand and Cuba (195, 196) These vaccines are immunogenic, but require multiple doses, especially in young infants, and efficacy appears to have a short duration of protection (197) Efforts to find novel vaccine antigens to protect against serogroup B disease have identified several protein surface antigens. Two vaccines that target these antigens are currently under investigation in clinical trials. These vaccines may have the potential to protect not only against serogroup B disease but against other serogroups as well. Preliminary data from these vaccines are promising, but the role these vaccines will play in controlling meningococcal disease remains to be determined.

**IV. Cost effectiveness of vaccine and cost of disease**

Data on the cost of vaccine and financial burden of disease is available from Africa and some developed countries where a vaccine has been introduced. Limited data on meningococcal carriage and incidence is available from other countries, especially in Asia, and thus cost effectiveness cannot currently be accurately determined for these countries.

**Cost effectiveness of vaccines in Africa**

In early 2000, the need for an affordable and highly immunogenic conjugate vaccine against Men A was highlighted jointly by a WHO expert group and African public health professionals.(170) In June 2001, the Bill and Melinda Gates Foundation agreed to fund the Meningococcal Vaccine Program, which is a 10 year partnership between WHO and PATH with the goal of eliminating epidemic meningitis as a public health problem in sub-Saharan Africa through the development, testing, licensure and widespread use of conjugate meningococcal vaccines. This contributed to the development of MenAfriVac™ vaccine (PsA-TT) by Serum Institute of India, which is a Men A polysaccharide (PsA) conjugated to a protein carrier, tetanus toxoid (TT). This vaccine obtained marketing authorization in India in 2009 and WHO prequalification certification in June 2010. GAVI has committed to fund a one-time vaccination campaign, but indicated that the expense of booster doses or incorporation of the MenAfriVac into EPI programs must be borne by the public health systems of participating countries.
Cost of disease and impact on health systems in Africa

One study in Burkina Faso found that the cost per household of a case of meningococcal disease in Sub-Saharan Africa is US$ 90 and an additional US$154 if sequelae of the disease occur. The urban cost is more than 200% higher than the rural cost. An idea of the overall burden of disease can be gauged from the total cost of the 2006-2007 outbreak, which was US$ 9.4 million, 7.1M borne by the public health system and 2.3M borne by households which comprised 34% of the GDP capita (198) The Meningitis Vaccine Project has the potential to:

- Prevent 123,000 deaths by 2018
- Prevent permanent disability in 287,000 children and adults
- Prevent 11 million DALYs lost
- Save approximately $99.7 million in medical costs for diagnosis and treatment

For Africa, a model was developed by Parent du Chatelet in 2001 in Senegal, which compared two vaccination strategies: vaccination with men A+C polysaccharide vaccine when epidemic thresholds are exceeded and alternatively mass preventive vaccination before outbreaks occurred. The model predicted prevention of 59% of the cases using a pre-emptive strategy compared to 49% for the emergency reactive strategy. The cost per case prevented was US$59 for the preventive strategy and US$133 for the reactive strategy, and the preventive strategy saved US$0.20 per habitant. Preventive meningococcal vaccination through mass campaigns prevented more disease at a lower cost, provided that the occurrence of an epidemic could be predicted within 3 years and that the vaccination coverage rates for the preventive and reactive strategies were > 70% and < 94%, respectively. (199) This model recommended mass preventive vaccination, especially for areas with poor surveillance systems.

Cost effectiveness of Men C conjugate vaccine

Six countries undertook economic evaluations around the introduction of MCC vaccines (Australia, Canada (Quebec), The Netherlands, UK, Portugal and Switzerland). All recommended that one dose in the second year of life was more cost-effective than a three-dose infant schedule (200).

Further development of the dynamic model was undertaken after vaccine introduction to predict the impact of the meningococcal vaccination program and its cost effectiveness in the UK. Various factors feed into this dynamic model, including the high transmissibility of the disease, the role of carriage/colonization and possibility of recurrent colonization with different serotypes, interaction between related bacteria, and the differing risks of colonization and disease at different ages. The model accurately reflected the trends of meningococcal disease in the UK when it was applied retrospectively to the actual experience in the UK from 1998 to 2004. It was also able to predict the significant herd protection that is being seen with the use of this vaccine. The UK model was also used to investigate the impact of vaccine schedules in the UK and Spain. (201) The catch-up campaign differed between Spain, where the upper age limit was 6 years in most autonomous regions, and the UK where a broader age range (up to 25 years of age) was
targeted. The latter approach was more effective in reducing disease, because both the direct and indirect effects were larger. Consistent with the observed results, the model predicted that herd protection effects for the Spanish strategy would be small (since 0-5 year olds rarely carry meningococci) and that by targeting teenagers, who are the most common carriers of meningococci, much greater herd protection could be achieved.

The major application of this model is in selecting the most cost effective modification that could be made in the meningococcal immunization program. Models can be used to inform decisions around introduction of meningococcal vaccines. These models must be adapted to the local epidemiology including serogroup distribution, age specific attack rates and nasopharyngeal carriage.
V. Fractional doses

Immunology

In recent years there has been concern that in the event of a large scale epidemic, the supply of the meningococcal vaccines may not be enough to match the demand. Thus, a trial was conducted to test the hypothesis that fractional doses of ACWY meningococcal polysaccharide vaccine confer for each serotype in the vaccine an immunogenic response, which is non-inferior to the full dose licensed vaccine(s) in the population targeted during mass vaccination campaigns in Africa. The objective of the trial was to measure the immunogenicity of each component of a dose corresponding to 1/5th and 1/10th of the amount of the current licensed vaccine. This was a randomised, single-blind, non-inferiority trial, in which healthy subjects aged 2 to 20 years in Uganda were enrolled. The study subjects were divided into three groups, with one group receiving a normal dose of the ACWY polysaccharide vaccine, a second group receiving 1/5th of the normal dose and the third group receiving 1/10th of the normal dose. An rSBA titer of >= 1:128 was considered to be a marker of immunity. A non inferiority margin of 10% between “full dose” and each study arm was selected.

The intent to treat and per protocol analysis included all participants, irrespective of the baseline seropositivity status. However, a subgroup analysis was also done on subjects who were not immune to the particular meningococcal serotype at baseline, i.e. before the vaccine administration (SBA <1:128). In the non-immune population, the immunogenicity of the 1/5th dose for serogroups A, W135 and Y was non-inferior compared to full dose. In the ITT and PP analysis, the immunogenicity of 1/5th dose for serogroups W135 and Y was non-inferior compared to full dose. The immunogenicity of 1/5th dose was inferior to full dose for serogroup C. With the 1/10th dose, the antibody titers generated were lower compared to 1/5th dose, however, it was still non-inferior to full dose for serogroups W135 and Y.

In the event of an acute shortage of meningococcal vaccines during an epidemic, 1/5th or 1/10th of the normal dose of ACWY polysaccharide vaccine can be considered depending on the serogroup causing the epidemic. However, since the absolute titers generated by the fractionated doses are lower compared to the full dose, the duration of protection provided by the fractionated doses is likely to be shorter than the full dose.

Feasibility

The International Coordinating Group, a collaboration between MSF, WHO, Red Cross and UNICEF, maintains a bank of meningococcal vaccines for public health emergencies. For the next year, there are approximately 10 million doses of Men AC/Men ACW vaccine and 3 million
doses of Men A conjugate vaccine in storage. At the time when 1/5\textsuperscript{th} dose was considered, the vaccine supply situation was much tighter. Now in addition to the vaccine stock pile, there are 10-15 million doses available in the marketplace as well. Hence there are around 25 million doses available in total for 2010/11. The WHO is currently satisfied with the supply for dealing with the next epidemic.
VI. Research needs on immunization against meningococcal disease

- Surveillance research needs

1. Epidemiological data on burden on invasive meningococcal disease is lacking from some parts of the world, especially Asia. Primary data on disease incidence is needed in these countries. In many countries where data exists, it remains suboptimal with especially limited laboratory confirmation.

2. Although no significant evidence of replacement disease has yet been seen, the possibility still exists. However, replacement disease should be differentiated from unmasking of secular trends that may be seen following improved surveillance and decrease in the vaccine prevalent serogroups. Timely surveillance and monitoring using molecular epidemiology tools can prevent outbreaks from unexpected strains.

3. Increased surveillance for IMD and meningococcal carriage in the times following Hajj is recommended in all countries, especially in countries from where a large number of people participate in this event.

4. Impact of meningococcal vaccines in the HIV positive population should be specifically studied.

5. Duration and breadth of protection, as well as effect on carriage/herd protection needs to be evaluated in countries (especially the meningitis belt countries) which have introduced meningococcal vaccines in their routine immunization program. Such studies should guide/validate need for booster doses and cost effectiveness of a certain immunization routine.

- Vaccine research needs

6. Consideration should be given to making a single vaccine formulation which combines meningococcal vaccines with the existing pentavalent vaccines. Another consideration is to make a single ‘meningitis vaccine formulation’ which combines S. pneumoniae, H. influenza type b and N. meningitidis.

7. Comparative immunogenicity of multivalent, bivalent, and monovalent conjugate meningococcal vaccines should be compared against each serogroup in order to make informed decision about the choice of vaccine to be used in a particular setting.
8. Fractionated doses of polysaccharide vaccines have been effective. Similar studies on conjugate vaccines can answer the question of whether it would be feasible to use the fractionated doses of quadrivalent conjugate vaccines on a mass scale in relevant countries.

9. Newly developed MenB vaccines using multiple conserved proteins conjugated with OMVs are promising. Data on safety and immunogenicity in infants, children and adults has been demonstrated for the Novartis vaccine; however persistence of antibodies and evidence of broad protection still needs to be evaluated. (202, 203) Studies to address these are highly recommended.
Recommendations

1. For all countries, knowledge of meningococcal disease burden is critical to making appropriate use of its vaccine. All countries considering the use of meningococcal vaccines should develop the surveillance infrastructure for meningococcal disease. This infrastructure should include both clinical case detection as well as laboratory capacity to diagnose and characterize *N. meningitidis*.

2. The ongoing MenAfricVac roll out plan should be used to strengthen the routine EPI program as well as the meningococcal disease surveillance infrastructure in these countries.

3. In countries where mass vaccination of 1-29 years old is being conducted under the MenAfriVac roll out plan, it is recommended that after the campaign, MenAfriVac be administered as part of the routine vaccination of young children in order to ensure continued protection. Currently MenAfriVac is only licensed in children older than one year of age, however studies to demonstrate its safety and immunogenicity in infants are at advanced stage. It is therefore recommended that after the campaign, MenAfriVac be given to all children 1-2 years of age on routine basis in these countries. This recommended age may be revised if MenAfriVac gets approved for use in younger infants.

4. Impact of the MenAfriVac vaccination campaign on the immunization and health care system, should be measured in African meningitis belt, using the tools under development and recommended by SAGE.

5. Countries with high endemic rate of IMD (as classified in the background document) should use an appropriate meningococcal vaccine in their population. The recommended strategy for the vaccine use is initial mass vaccination of the population 1-29 years of age, followed by the inclusion of meningococcal vaccine in the routine vaccination programs for the infants. Continued surveillance of IMD should dictate the need and timing of repeat mass vaccination campaign.

6. Countries with intermediate endemic rates of IMD (as classified in the background document) may choose to use the appropriate meningococcal vaccine in their population. If so, similar approach to introducing meningococcal vaccines is recommended in these countries as has been described above for highly endemic countries.

7. The choice of vaccine for each country should depend on the serogroup(s) (or serosubtype in case of serogroup B) of *N. meningitidis* that are locally prevalent. In general, conjugate vaccines are preferred to polysaccharide vaccines due to their impact on decreasing nasopharyngeal carriage of *N. meningitidis* and their overall increased immunogenicity in children. Nonetheless, polysaccharide vaccines are also acceptable especially when individual level protection (as opposed to population level protection) is desired e.g. for the military recruits, during Hajj and during an outbreak.
8. Further research in the development and testing of protein based vaccines against serogroup B is highly encouraged, as these vaccines have the potential to be cross protective against all meningococcal serogroups.

9. During an outbreak, vaccine which covers the prevalent serogroup (or serosubtype in case of serogroup B), if available, should promptly be used in a mass vaccination campaign. While appropriate monovalent vaccines, when available, are recommended for such mass campaigns, multivalent vaccines potentially offer additional benefit in those countries that have a substantial amount of disease due to more than one serogroup if their immunogenicity against outbreak causing serogroup is as good as the monovalent vaccine and the price is in an acceptable range.
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