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Meningococcal Vaccines

Current Status and Future Possibilities

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Summary

Meningococcal disease causes great emotion and anxiety in the families and caregivers of patients. Numbers of such patients are usually small in industrialised countries, unlike those in many regions – especially in subsahelian Africa. Vaccines have been tried for more than 80 years; at present there are available polysaccharide vaccines against groups A, C, Y and W$_{135}$, and a protein-based vaccine against group B. A property common to all is their relative efficacy (75 to 100%) at school age and after, and an acceptably short persistence of antibodies. Small children pose the major challenge, in whom there is essentially evidence of clinical protection only against group A and C diseases. With vaccines against other serogroups protection is possible, but not yet proven in controlled clinical studies. The search is on for help from various modifications, including the conjugation technique, to transform the independent nature of polysaccharide response towards T cell dependence, as was done earlier in *Haemophilus influezae* type b vaccines. First trials along this path are encouraging although, again, group B

meningococci pose special problems. The next few years will probably see a new generation of meningococcal vaccines.

Generally speaking, the incidence of meningococcal disease is too low to indicate vaccinations for the whole population, or even children, but some risk groups and epidemics are important exceptions. To date, bivalent group A + C or tetravalent group A + C + Y + W_{135} polysaccharides, or an outer membrane protein-based group B vaccine, are the products to be used when the indications, that may vary from country to country, are considered met. A strong herd immunity effect, demonstrated with group A and C vaccinations, facilitates extinction of an epidemic since large-scale vaccinations can be restricted only in the major risk groups, children and in various schools. Prompt intervention demands, however, a functioning mechanism which detects very early on a pending epidemic. Unfortunately, such a mechanism is often lacking in countries often hit by this deadly disease.

Disproportionate public attention[1] to meningococcal disease (due to *Neisseria meningitidis*) in industrialised countries – a few cases are characterised as an 'outbreak',[2,3] while tens of thousands of people fall ill in repeating epidemics in subsaharan Africa[4-6] – reminds us that meningococcal disease is still with us.[7]

One-third of cases occur at ages 0 to 4 years, one-third among 5- to 19-year-olds, and one-third at age 20 and later.[8] Special risk factors include living in the subsahelian 'meningitis belt',[4] or being a military recruit,[9] alcoholic,[10] or participant in a large pilgrimage.[11] In Africa, epidemics may reach disastrous proportions, with attack rates approaching 1% of the population.[4,12]

The standard 'cerebrospinal fever' is not the only problem, as even greater fatality rates are caused by meningococcal septicaemia. Sometimes, these 2 entities occur together. Innovations in treatment of fulminant meningococcaemia are needed urgently,[13] as are better vaccines for the whole complex disease with its various manifestations (figs 1 to 3).

1. Natural Protection from Meningococcal Disease

To understand meningococcal disease and the philosophy behind the development of vaccines, an outline of immunology needs to be given. *N. meningitidis*, a human pathogen only, is divided into 12 (or 13) serogroups according to their outermost structure: capsular polysaccharides (linear homopolymers) A, B, C, 29E, H, I, K, L, W_{135}, X, Y and Z. These polysaccharides are specific to each serogroup, and essential to pathogenicity. The group A (MenA) polysaccharide is composed of *O*-acetylated residues in the 3 position of mannos-

Fig. 1. If meningococcal disease manifests as meningitis and septicaemia (*Neisseria meningitidis* identified in cerebrospinal fluid and blood or, especially, in blood only), fatality rates increase considerably over those for meningitis only. Shown here is an infant with *N. meningitidis* Group C (MenC) disease.

Fig. 2. The ultimate cause of death in fulminant meningococcaemia is often suprarenal haemorrhage (Waterhouse-Friederichsen syndrome), caused here by MenB disease.

amine-6-phosphate linked to α(1→6), while the group B (MenB) polysaccharide is a homopolymer of α(2→8) *N*-acetylneuraminic acid. The group C (MenC) polysaccharide is more variable: it comprises *O*-acetylated residues in the 7 and/or 8 position (in *O*-acetyl-positive form), or is made up of nonacetylated (in *O*-acetyl-negative form) *N*-acetylneuraminic acid linked α(2→9). If necessary, further typing of the different strains is possible by taking into consideration the different outer membrane proteins.

Over 90% of cases of meningitis are caused by serogroups A, B and C. All cause epidemics, but most are characteristically caused by MenA. In Europe and Latin America, group B is usually most prevalent, causing well over 50% of cases, whereas in the US and Canada MenC is the commonest.[2,3] A virulent clone, ET-15, seems to be increasing in importance.[14]

By the second decade of this century it had been demonstrated that serum therapy decreased the fatality of meningococcal meningitis,[15] and it was suggested that serum antibodies would play a role in protection. The theory proved right: natural protection is achieved mainly by development of anticapsular antibodies, though less so in MenB disease. The 1960s showed an inverse relation between ‘functional’ bactericidal antibodies and susceptibility to disease.[16]

Natural immunisation to meningococcal disease is thought to be caused by nasopharyngeal carriage of *N. lactamica* or other nonpathogenic Neisseriae.[17] However, the parallel rise in specific anti-A or anti-C capsular polysaccharide antibodies, measured by sensitive radioimmunoassay,[18,19] is not explained by such carriage –

Fig. 3. Skin necrosis, which may require reconstructive surgery, is characteristic of meningococcal septicaemia. This patient presented with MenA disease.

assay,[18,19] is not explained by such carriage – these Neisseriae do not have a capsule. Since the carriage rate of virulent meningococci is too low to confer immunity,[17,20] natural immunisation probably occurs through unrelated but serologically cross-reactive bacteria. *Escherichia coli* K1 has a polysaccharide structurally and serologically identical to that of MenB meningococci.[21] From the age of 2 years onwards antibody concentrations increase, so that each year 5% more children have serum bactericidal activity against MenA, B and C meningococci. Intermittent carriage of different serotypes broadens immunity. Carriage of all meningococci is highest in young adults; military recruits develop a marked increase in bactericidal titre of immunoglobulin G (IgG), IgM and IgA antibodies within the first few weeks.[21]

Several questions still remain unanswered, especially in MenB disease. MenB polysaccharide is poorly immunogenic in humans.[22,23] There is a fear that using this polysaccharide as a vaccine would hide risks of immunological tolerance because the homopolymer of $\alpha(2\rightarrow8)$ *N*-acetylneuraminic acid might cross-react with polysialic acids of embryonic neural cell adhesion molecules: perhaps an autoimmune process would be triggered, and vaccine-induced antibodies might interfere with the functions of the polysialylated protein components of the brain.[24] The relevance of the theory has been questioned,[25] but since it is very difficult to prove (or disprove), it has blocked much of the research on MenB polysaccharide. Nevertheless, anti-MenB polysaccharide antibodies (those few that are induced) are bactericidal in the presence of human complement.[26]

2. First Vaccines

A grim epidemic of 'cerebrospinal fever' elicited attempts to prevent disease with whole cell and autolysate vaccines as early as in 1907-1912 in New York.[27] Trials also were carried out in the Sudan in 1915, among US and British troops before and during during World War I.[28,29] Later, in 1930, vaccination programmes were carried out in the Sudan and Uganda, where a trend towards protection was observed.[28] The most encouraging results were reported from Chad and the Central African Republic in 1936-1939.[30,31] In Chad, only 1 case of the disease was found among 5000 persons administered vaccine (two-thirds of the population) *vs* 23 cases in the one-third of the population that was not vaccinated.

This study showed that immunisation against a much-feared disease was possible. However, the discovery of sulphonamides deflected interest in vaccines until emerging drug resistance induced further research. A polyvalent whole-cell vaccine against MenA (and to some extent against groups B, C and D) was tested in a World Health Organisation (WHO)-sponsored trial in Upper Volta (now Burkina Faso) in 1966-1967.[32] However, the number of cases was too small for conclusions, although the study was repeated.

3. Polysaccharide Vaccines (MenA, MenC, MenW$_{135}$, MenY)

3.1 Background

The door to better vaccines was opened by pneumococcal polysaccharides, which induced a good seroresponse and prevented pneumonia.[33,34] Using the same technology, MenA meningococcal polysaccharide was purified and tested in volunteers.[35] It did not work – and the study was forgotten. It later turned out that the molecular weight of that polysaccharide had been too small (less than 20 000D, instead of 80 000D or greater) to induce good seroresponse.[36] When the purification method was modified, immunogenic preparations were obtained both for MenA and C disease.[37] Now a polysaccharide vaccine is available against groups A, C, W$_{135}$ and Y strains.

Inadequate molecular weight was not the only problem in the development of meningococcal polysaccharides. The first field trial with MenA vaccine in Africa yielded disappointing results.[38] Fortunately, the researchers did not give up, because, as it turned out, it was too high a storage temperature that had depolymerised the vaccine.[23] Since then, the track for polysaccharides has been smoother. Polysaccharide vaccines are easy to manufacture, and they are well tolerated. Their main disadvantages are poor immunogenicity in infancy, except for MenA, and high group specificity. Hence, bivalent A + C and tetravalent A + C + W_{135} + Y vaccines have been developed.[39-46] For the reasons given above at the end of section 1, no MenB polysaccharide vaccine exists.

3.2 Immunogenicity

Generally speaking, the older the individual (until reaching adulthood) is receiving the vaccine, the better the polysaccharide seroresponse, which cannot be much improved with higher doses. Most trials in humans have used 50μg of each polysaccharide (varying from 25 to 50 μg),[18,45] although doses of MenC polysaccharide have varied between 10 and 100μg; antibody concentrations have not varied much.[9] Hence, there seems no reason to deviate from the generally accepted dose of 50μg, except perhaps for MenC because, interestingly enough, one-fiftieth (1μg) of the usual dose of MenC polysaccharide seems more immunogenic than the traditional 50μg.[47] Subcutaneous routes are routinely used, but intracutaneous injection has been practised both experimentally[23] and in the field (jet gun).[38,48,49]

3.2.1 MenA

MenA polysaccharide is more immunogenic than C in infants and small children.[45,50] Practically all adults seroconvert, i.e. antibodies rise from nondetectable to detectable, or they rise at least 2-fold from baseline values.[18,50] In contrast to other polysaccharides, an anamnestic response occurs at age 2 to 3 years with a mean antibody concentration at around 15 mg/L, which is not far from the adult mean of about 20 mg/L.[18] This explains why MenA disease is rare after vaccination, although an estimated 36% of adults remain, at least in principle, at risk because of a lack of bactericidal antibodies.[16,51] Infants of <6 months of age produce a weak response, but this can, at least to some extent, be boosted.[18,45] MenA vaccine can obviously be used earlier in life than other polysaccharides.[18,45,52] Hence, the decline of antibodies is slower than for MenC.[45]

3.2.2 MenC

MenC polysaccharide vaccine behaves differently. The response both to polysaccharide vaccine and MenC disease is better related to age. Two-year-olds respond with an antibody concentration about 10% that of adults, in whom the vaccine produces mean levels exceeding 30 mg/L,[50] close to those induced by MenA vaccine. An increase in bactericidal antibody occurs in around 50% of infants and 75% of children with a slightly better response to an *O*-acetyl-negative polysaccharide than to a positive one.[45] A similar anamnestic response to that with MenA polysaccharide does not occur, even in adults,[47,53] among whom the response varies depending on the extent to which the first dose induced antibody production.[45,54] Repeated doses restore the concentration to the levels to those previously achieved, in most.

Hyporesponsiveness to MenC polysaccharide of infants and small children, especially if doses are repeated, has raised questions.[40,47,53,54] The first dose induces a response in infants.[45,52] In a recent study among 12- to 20-month-old children, quadrivalent A + C + W_{135} + Y vaccine produced titres of 6.24, 4.81, 1.45 and 3.32 μg/L, respectively.[52] In an older study, a second dose of quadrivalent vaccine 12 months later resulted in a good response in bactericidal antibodies also among infants who had been only 3 months old when first immunised.[45] Furthermore, infants born to mothers vaccinated during pregnancy have responded well to the A and C polysaccharides.[55] On the other hand, when children at age 15 to 23 months received 2 doses (2 months apart) of MenC polysaccharide, MenC conjugate or hepatitis B vaccine, a polysaccharide challenge 12 months later induced anti-C bactericidal antibodies at a level of 1 : 8 or higher in 18, 100 and 53%, respectively.[56] Thus, MenC polysaccharide induced some tolerance, detectable a year after vaccination.

The question remains whether these findings would have been otherwise with a significantly smaller dose of polysaccharide.[47] Furthermore, the practical relevance of the data awaits future studies, but they certainly curtail enthusiasm for immunising children with MenC polysaccharide, at least in nonepidemic conditions. In epidemic conditions, starting vaccination, even with traditional dosing, might be well reasoned (section 3.6.2).

3.3 Protective Antibody Levels

Knowing exactly the protective antibody levels for each meningococcal group would facilitate estimates of the persistence of protection. However, the issue is not fully settled.

3.3.1 MenA

Protection from disease is probably achieved with an antibody level of about 2 mg/L,[18,57] which is 10-fold higher than the 0.2 mg/L deduced from agammaglobulinaemic patients.[58] As is the case with *H. influenzae* type b (Hib) disease, it is possible that the concentration necessary for protection is dependent on whether it is induced by vaccination or naturally; in the latter case, a lower level suffices.

3.3.2 MenC

Equivalent information for other meningococci is lacking. We may assume that the same concentration, ≈2.0 mg/L, also applies to MenC. In Brazil, children who were 75% protected had a geometric mean titre at this level after vaccination, whereas those given vaccinations aged 2 years or less, who responded with less antibody, were not protected.[59]

For other serogroups even this information is not available.

3.4 Duration of Protection

3.4.1 MenA

Vaccinations to those in the age group 0 to 1 year have levels of their anti-A antibodies return to preimmunisation levels within 2 years, regardless of whether they have been vaccinated once or twice. With increasing age, the antibody concentration declines less and less steeply. Extrapolation from the mean concentration of 7.88 mg/L, measured 3.5 years after vaccination at age 13 to 14 years, suggests that elevated levels of anti-A antibodies may persist for about a decade.[60] We may assume that protection for a period of 1 to 10 years can be expected, depending on the age at which vaccination was performed. Retrospective data from Saudi Arabia suggest that pilgrims lost protection if more than 5 years had elapsed.[61]

Small children do less well, at least in Africa.[62,63] In Burkina Faso, a case-control study showed that for those immunised with A + C vaccine at age 0 to 3 years, a decline in crude efficacy against MenA declined from 100 to 8% within 3 years; for the age group 4 to 16 years, the figures were 85 and 67%, respectively.[62] Unfortunately, only one vaccine dose was used, which left unanswered the important question whether longer protection would have been achieved with a booster dose. Of relevance in the tropics is the observation that chloroquine treatment a week before vaccination improves the response[64] because the immunologically depressive effect of malaria[65] is transiently mitigated.

3.4.2 MenC

Vaccinated infants lose MenC polysaccharide antibodies to baseline levels within 3 to 5 months.[66] Children do somewhat better. When individuals aged 6 months to 19 years were vaccinated with quadrivalent vaccine in Canada,[67] antipolysaccharide concentration had increased 113-fold (mean 7.56 mg/L) 1 month after vaccination; 68% of infants at age 6 to 11 months, and 85% of others vaccinated, showed a mean concentration at or above 2 mg/L. In 12 months the overall concentration declined to 3.03 mg/L, but this was still significantly greater than before vaccination. Children younger than 18 months showed a steeper decline in antibody concentrations.

The mean titre of bactericidal antibodies in the whole group rose from the initial 1.17 to 33.5 titres one month after vaccination, and to 22.2 one year later. Capsular antibody concentration seemed to reflect bactericidal antibodies, but only from age 18 months on. However, 3 years after vaccination, a significant decline in polysaccharide and bactericidal antibodies had occurred among those aged 6 to 24 months when vaccinated.[68] This suggests that this age group had perhaps been unprotected, a similar concern which has been applied to adults.[47] A booster dose given 3 years from the primary vaccination was associated in one study[67] with a greater geometric mean titre but a lower percentage of children achieving a threshold response. The finding is relevant to the finding of a lower booster response to MenC polysaccharide compared with children vaccinated for the first time with the same vaccine.[56]

Adults have been thought to retain MenC antibody better than children because, after a 5-year follow-up, they showed concentrations around 30% of the postvaccination peak.[69] However, in another study, all adults showed undetectable MenC bactericidal titres 4 years after vaccination, and only 1 of the 5 volunteers responded weakly to the booster.[53] There is clearly a need for more data; for example, would MenC polysaccharide behave more favourably with much smaller doses (1μg)[53]?

3.4.3 MenA + C

Four years after bivalent A + C immunisation of a mixed paediatric-adult population, titres obtained by haemagglutination technique related to the 2 mg/L level of radioimmunoassay were still measured in 75% for MenA and 72% for MenC in Nigeria.[70] Dutch investigators[71] have proposed that, in adults, the IgM : IgG ratio is important; the lower it is 14 days after vaccination, the longer the MenA and C antibodies persist, reflecting a relatively well developed memory system (IgG-producing memory B-cells are triggered). Quadrivalent MenA + C + W_{135} + Y vaccine has been used in the US army since 1982, and an analysis of groups A and C was accomplished a decade later.[72] One month after vaccination, MenA antibodies had increased more than 11-fold (mean 13.4 mg/L); they then decreased 65% in 2 years, but were still 27% of the maximum 10 years later. For MenC, a 39-fold increase (mean 25.7 mg/L) occurred initially, followed by a 76% decrease in 2 years. After 10 years, the level of 2 mg/L or greater was measured in 75% of those originally vaccinated for MenA and 85% for MenC. Bactericidal antibodies against MenC were determined; they were also detectable, albeit in low titres. It is likely that at least some degree of protection against both groups had lasted at least a decade.

3.4.4 MenA + C + W_{135} + Y

Data on the persistence of the groups W_{135} and Y antibodies are scanty. In a Finnish study,[45] infants aged 6 to 23 months were vaccinated twice (12 months apart). Good bactericidal response against all 4 components was achieved within 2 weeks. However, the levels soon declined, except for group W_{135} which maintained and kept the induced levels geometric mean titre in $\log_2$ (GMT in log2) of between 5 and 6 almost unchanged for 12 months after vaccination in the 6- to 11-month-olds. The second dose reinduced bactericidal antibodies to the concentrations reached originally, also in MenC (peak at 9 GMT in log2), without findings suggestive of tolerance.[47] In agreement with another report,[52] no true booster response was observed.

A challenging finding in the most recent trial,[56] that a third MenC polysaccharide dose did not alter the antibody level, is in need of explanation. There is a need for standardisation of the laboratory techniques since, for example, low-avidity antibodies are bound especially well by enzyme-linked immunosorbent assay (ELISA). More research is warranted on this issue.

3.5 Tolerability

Except for the only double-blind study, in which MenA meningococcal and Hib polysaccharides were compared side by side in the 1970s,[18,57] no equally objective information on reactogenicity of the vaccines is available. When the studies were done in the 1970s, local reactions or fever of at least 38.5°C (101.3°F) were found in association with meningococcal polysaccharide in 71 and 1.8% of those administered vaccine, respectively. The incidence of fever declined to 0.5% when vaccine lots with less endotoxin came into use. Among 21 000 infants and children, only 3 cases with

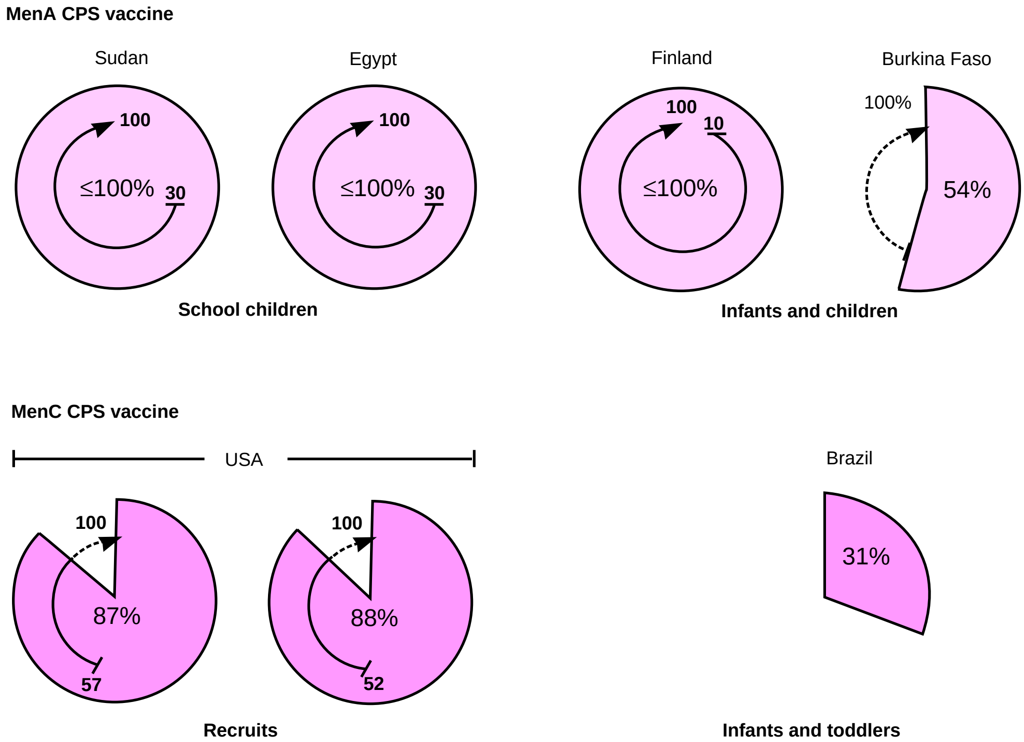

Fig. 4. There have been few controlled studies with meningococcal capsular polysaccharide (CPS) vaccines, but those that have been reported show reasonable effect among children and adults. The percentages indicate the efficacy; bold numbers show the estimated 95% confidence intervals (CI_{95}). In Burkina Faso, the initially good efficacy declined to 54% within 4 years.

probable allergic reactions were found, and among 1.2 million persons administered vaccine aged 3 months to 19 years, possible anaphylaxis occurred once per 100 000 vaccinations.[57] All symptoms and signs subsided after treatment with corticosteroids or adrenaline (epinephrine). Since the endotoxin content of current vaccines is a fraction of that in the vaccines in use at that time, adverse effects are now rare.

Increasing the number of antigens in same vaccine does not increase reactogenicity significantly.[40-46,72] In association with quadrivalent vaccine in Canada,[68] fever was reported in less than 1%, local reactions in 6.3% and rash in 1.6% among those aged 11 years or older. A preponderance of local reactions is also noticeable in other reports.[73]

3.6 Clinical Efficacy

The fear engendered by meningococcal disease has triggered a number of observational surveys on the impact of vaccination, but there is only a handful of efficacy studies with an adequate control group (fig. 4). In addition, the follow-up has usually been very short, over one epidemic or so. Hence, the case numbers have remained small. However, there are still reasonably good grounds for the statement that MenA and C polysaccharides work – albeit with certain restrictions.

3.6.1 MenA

MenA vaccine was first studied among school children in Nigeria,[38] Egypt[48] and the Sudan[49] (table I). The efficacy was approximately 80 to 90%, except in Nigeria (where tropical heat had destroyed the vaccine[23,38]). The trials were soon continued in Europe[51] and Asia.[74] The study in the Finnish defence forces was important for 2 reasons: it not only demonstrated efficacy in adults (84%) but also a clear herd immunity; when 40% of recruits had been vaccinated, MenA disease disappeared.[51] This information was soon successfully exploited throughout Finland, so that the MenA epidemic waned as a result of vaccinating only children and young people (≤20 years), 1.2 million people in all.[83]

The only successful and double-blind study to date was carried out among 100 000 infants and children in Finland in the mid-1970s.[18,57] After 12 months, no cases of MenA disease occurred among the specifically vaccinated *vs* 6 cases in the control group (and 13 cases in those who were not vaccinated).

Several epidemics have been extinguished by vaccination since over the past quarter century (table I). The New Zealand study[80] clearly showed the necessity of 2 doses for children younger than 2 years.

The experience of pilgrims to Makkah (Mecca)[81] demonstrated that effective mass vaccination was also feasible in hectic, crowded and warm conditions. However, equal success was not met with in a refugee camp in Zaire.[84]

3.6.2 MenC

MenC polysaccharide was the first vaccine with proven efficacy, in US army recruits[9,85] (table II), where an 87% efficacy was demonstrated during a 3-year follow-up (fig. 4). The impact of vaccination has been clear among Italian air force recruits – 91% effectiveness[86] – in the UK Royal Air Force,[87] in outbreaks in school[88] and among students.[89] In an outbreak in Texas, an effectiveness level of 85% was found in a case-control study.[90] The most conclusive results of various studies are listed in table II.

Table I. Efficacy studies on *N. meningitidis* group A polysaccharide vaccine (mostly using a bivalent serogroup A+ C)

Country, year	Study population		Design	Follow-up	Cases		Efficacy (%)	Estimated 95% CI[a]
	no.	age			vaccinees	controls		
Nigeria 1971[38]	14 000	5-15y	Placebo-controlled	Months	8	5	61[b]	–203; 87
Egypt 1971-2[48]	120 000	Schoolchildren	Controlled	6mo	0	8	≤100	≈30; 100
Sudan 1973[49]	20 000	Schoolchildren	Controlled	≈4mo	0	7	≤100	≈30; 100
Finland 1974[51]	37 000	Recruits	Open	9mo	1	8	84	≈10; 100
Finland 1974-5[57]	100 000	3mo-5y	Double-blind	12mo	0	6	≤100	≈10; 100
Mongolia 1974-5[74]	35 000	0-8y	Observational	6mo			Probable	
Nigeria 1977-80[75]	2.5 million	Variable	Observational	≈3y			Likely	
Nigeria 1979[76]	20 000	≥1y	Observational	3mo	2	38	93	61; 100
Mali 1981[77]	270 000	1-30y	Open	Epidemic period	29	126	84	64; 100
Burkina Faso 1981[62]	13 000	3mo-16y	Case-control	1, 2, 3y			87, 70, 54	
Gambia 1983[78]	670 000	≥1y	Observational	24mo			78	35; 92
Nepal 1984[79]	330 000	1-24y	Observational	14mo			82% decrease in disease	
New Zealand 1987[80]	≈17 000	3mo-13y	Open	2.5y	0	9	≤100[b]	
Saudi Arabia 1992[81]	60 000	Pilgrims	Observational	Months	9	76	83	50; 94
Mongolia 1994[82]		2-8y	Case-control	1y	54	156	92	76; 97

a Lowest theoretical efficacy; highest theoretical efficacy.

b Vaccine destroyed by heat.

Abbreviation: 95% CI = 95% confidence intervals.

Table II. Efficacy studies on *N. meningitidis* group C polysaccharide vaccine (mostly using a bivalent serogroup A+ C vaccine)

Country, year	Study population		Design	Follow-up (mo)	Cases		Efficacy (%)	Estimated 95% CI[a]
	no.	age			vaccinees	controls		
US 1969[9]	68 000	Recruits	Randomised	2	1	38	87	57; 100
US 1969-70[85]	75 000	Recruits	Randomised	2	1	35	88	52; 100
Brazil 1972[91]	135 000	6–36mo	Controlled	17	31	45	NS[b]	
Italy 1987-89[86,92]	300 000	Recruits (18-25y)	Observational	12	1	11	91	≈10; 75
Australia 1990-91[93]	≈500	1–15mo (Aboriginal)	Observational	≈7			77	≈ –8; 95
Quebec, Canada 1992-93[94]	5.8 million	6mo - 20y	Observational	≈4y	11	35	79	53; 91
Czech Republic 1993[95]	≈10 000	15-19y	Observational	14	0	4	NS	
Gregg, Texas, 1994[87]		2–29y	Case-control	≈12	17	84	85	27; 97

a Lowest theoretical efficacy; highest theoretical efficacy

b Efficacy approximately 55% at age 24-36mo.

Abbreviations: NS = nonsignificant.

Efficacy data on children are scanty. In Brazil in the mid-1970s, the vaccine was reported as 55% protective in 24- to 36-month-olds, but not in infants of 6 to 12 months, in whom the incidence of disease was reduced by only 12%.[91] It was later shown that essentially no serum bactericidal activity (less than 1 : 4) is achieved with C polysaccharide before the age of 2 years, despite apparently adequate IgG levels (2.4 to 9.1 mg/L).[96] The Brazilian experience has in any case been a key factor backing the view that MenC polysaccharide should not be administered before the third birthday.

However, Australian Aboriginal children from 12 months old showed a benefit from vaccination in 1990-1992,[93] and an epidemic in a nursery has been controlled by MenC polysaccharide.[97] Most conclusively, not less than a 70% efficacy was observed among 6 month to 4-year olds in Quebec, Canada.[94] Clearly, *in vitro* data are not straightforwardly applicable to *in vivo* circumstances.

4. *Neisseria meningitidis* Group B Non-Polysaccharide (MenB) Vaccines

4.1 First Trials

The first MenB epidemic in which vaccination was tested was that in Khartoum and Omdurman, Sudan, in 1931.[28] Over 10 000 vaccinated individuals were compared in an open method with an equally large control group that had received typhoid vaccine. A trend towards protection was observed (table III). In 1981, South African children were exposed to a double-blind study in which MenB polysaccharide serotype 2 protein vaccine was compared with a group immunised with an A + C polysaccharide.[104] No conclusive results were obtained in this survey either. Since then, several attempts have been made to make a vaccine immunogenic enough to confer protection. In Iquique, Chile, one group used a vaccine against the epidemic strain B:15:P1.3 (serogroup:serotype:subtype), which included outer membrane proteins. A short-lasting 51% protection was achieved.[105,106]

4.2 Current Vaccines

4.2.1 Vesicle Vaccine (Norwegian Type)

A MenB epidemic that lasted over a decade in the 1970s-1980s forced authorities in Norway to try prevention by vaccination. Finally, in 1988-1991,[98] a placebo-controlled study with vaccine consisting of the whole outer membrane complex showed a 57% efficacy against the epidemic strain B:15:P1:7.16 in children of school age (table III). However, the randomisation method used (by school) has been criticised.[107] Although the efficacy was considered too low to justify the issue of a licence,[98] commercial production is still about to commence.

4.2.2 Outer Membrane Protein–Based Vaccine (Cuban Type)

Finlay Institute, Havana, has manufactured a bivalent vaccine in which C polysaccharide is added to a mixture of high molecular weight B outer membrane proteins and proteoliposomes (serotype-specific protein phospholipids) to enhance antibody production.[99,108] The vaccine is licensed in 20 countries, and has been used in tens of millions of doses, especially in Latin America. A double-blind study in Cuba among school children demonstrated 81% efficacy among 10- to 14-year-olds[99] (table III). The finding is important since, for the first time, it was demonstrated that antibodies elicited to noncapsular antigens prevent meningococcal disease.

Fairly good protection in older age groups has also been seen in other studies (table III), although difficulties remain with small children, for whom reliable information is lacking. A case-control study from São Paulo[100] estimated 47% protection at age 24 to 47 months (fig. 5) but, surprisingly, a negative 37% effect in children younger than 2 years. Another case-control study from Rio de Janeiro[102] concluded that effectiveness was 41 to 47% even in the youngest (6 to 23 months), the higher figure obtained in the capital itself. However, the methodology used has been heavily criticised,[101,103,109,110] and considerably different figures have been presented from the very same

Table III. Efficacy[a] studies on *N. meningitidis* group B non-polysaccharide vaccines vaccines. All figures given as percentages

	Age group (mo)			
	<24	24-47	≥48	schoolchildren
Historical vaccine [whole-cell]				
Khartoum and Omdurman (Sudan) 1931[28]				
efficacy against disease	31[b] (across all age groups)			
efficacy against death	38[b] (across all age groups)			
Outer membrane vesicle vaccine [Norwegian vaccine]				
Norway 1988-91				
clinical efficacy[98]				57
lower 95% CI				27
Outer membrane protein–based vaccine [Cuban vaccine]				
Cuba 1987-89[99]				
clinical efficacy				81
95% CI				44; 93
São Paulo 1990-91[100,101]				
clinical efficacy, all probable cases included	–37	47	74	
95% CI	≤100; 73	–72; 84	16; 92	
clinical efficacy, definite cases only included	5	53	73	
95% CI	–426; 83	–79; 88	2; 93	
Rio de Janeiro 1990[102,103]				
clinical efficacy	10-47[c]	41-69	71-82	
Santa Catarina (Brazil) 1990-92[103]				
clinical efficacy	55	62	78	
95% CI	–16; 83	14; 83	54; 90	

a Given in percentages.

b Across all age groups vaccinated.

c Depending whether laboratory-confirmed cases only (lower figures) or all probable cases (higher figures) were calculated.

Abbreviation: CI = confidence interval.

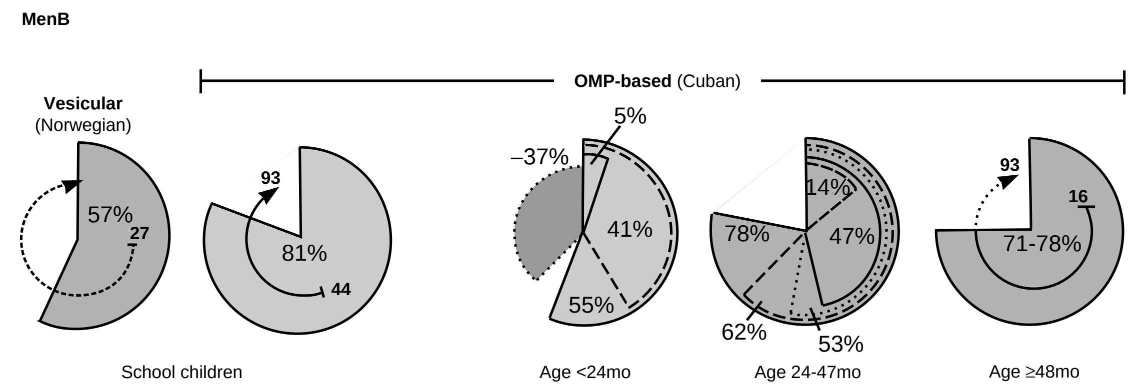

Fig. 5. Besides some historical whole-cell vaccines, 2 types of vaccine have been tried in meningococcal MenB disease. Both induce 60 to 80% protection from school age on, but the problem lies with infants and small children. No data exist on the Norwegian 'vesicular' vaccine, and estimates on the Cuban outer-membrane-protein (OMP)–based vaccine vary depending on how the data are dealt with (see section 4.2.2). The percentages indicate the efficacy; bold numbers show the estimated 95% confidence intervals (CI_{95}).

data (table III). The point is that these case-control studies fell into the hospital selection bias: if the Cuban vaccine also mitigates MenB disease (as it might), a larger proportion of those vaccinated with milder disease survived long enough to be referred to hospital and were reported, whereas those who died soon – case fatality could reach 54% at age 0 to 4 years[110] – were not included. This bias underestimated the true efficacy, even more so if only the laboratory-confirmed cases were counted.

This point was taken into account in Santa Catarina, Brazil. The vaccine protected children younger than 4 years from disease with a 59% (bacteriologically confirmed) to 68% (all probable cases) effectiveness – but seemingly also relieved disease in vaccine failures; the efficacy based on fatality rates was 76% (95% confidence intervals 44 to 90).[103,110]

The impact of vaccination was investigated among children younger than 6 years in Holguín, Cuba. The vaccine was considered responsible for at least 80% of the 98% reduction in MenB disease.[111] Concern has also been raised that the Cuban vaccine, being derived from the strain B:4:P1.15, might not protect against heterologous strains. The vaccine was effective in Brazil perhaps because one of the main epidemic strains was the same as in Cuba, B:4:P1.15.23. However, protection after the age of 4 years against other B strains suggests that the vaccine extends its efficacy to heterologous strains.

Serology has produced frustrating results since it is not clear which antibodies correlate with clinical efficacy, though the doctrine is that the vaccine must induce complement-dependent bactericidal antibodies.[112] An immunogenicity study among young adults in Iceland[113,114] did not show major differences between the Norwegian and Cuban vaccines. The titres against homologous strains were higher among recipients of the former, whereas the group immunised with the Cuban vaccine showed slightly better response to heterologous strains; this might explain why protection has been observed in sites outside Cuba (table III).

On the other hand, only 13% of children younger than 2 years in São Paulo[100] developed bactericidal antibodies (titre ≥1 : 4) *vs* 48% of those over 24 months[115] – perhaps this partially explains the lower effect in the youngest children (table III). Findings on the Norwegian vaccine suggest that giving 3 doses, instead of the recommended 2 (as with the Cuban vaccine), induces better production of bactericidal antibodies and might even broaden the spectrum to heterologous strains.[116]

Adverse reactions have been studied quite extensively with the Cuban vaccine.[117] Among 16 700 persons vaccinated, mostly older than 4 years, local pain was observed in 62%, and general reactions attributable to the vaccine in 4.3%. However, no serious reactions were detected.

While awaiting more conclusive studies with these 2 products, other vaccine approaches have been tried. Iron-binding proteins[118] and a vaccine of Class 1 outer membrane proteins (PorA)[119,120] have shown encouraging results. A recombinant vaccine, which is produced in *Bacillus subtilis* and reconstituted in phospholipid liposome,[121] protects infant rats from MenB meningitis.[122]

5. Conjugate Vaccines

Spectacular success with the protein-conjugate preparations of Hib vaccines[123] – which convert polysaccharides into T-dependent antigens and, hence, provide good booster effect and probably long term protection – challenges the research on meningococci.[124-126] Studies in humans are well under way.

5.1 MenA and MenC

Since MenA, W_{135} and Y diseases are rare in industrialised countries, and group B meningococci pose specific problems, investigators have first concentrated on producing monovalent C or bivalent A + C conjugates. As is logical, the same carrier proteins have been utilised as in Hib disease. First, A and C polysaccharides were independently coupled to atoxic diphtheria toxoid (CRM_{197}) carrier protein.[47,127] Immunoresponse in adults proved no better than with plain polysaccharides,[128] but after the conjugation method was modified, immunogenicity improved not only in adults but in toddlers and even infants.[56,129,130] All who received their first of 3 doses at age 2 months showed anti-MenA and C antibodies at 2 mg/L or greater after the second dose, and the concentration of these antibodies remained at that level for 12 months in 83 and 52% of patients, respectively. Bactericidal titres were measured for MenC, and the level of 1 : 8 or greater was achieved in all who were vaccinated; the situation continued for at least 1 year in 47%.[129]

Comparable findings were obtained in another study in the UK, in which monovalent MenC conjugate was administered 3 times, at 2, 3 and 4 months of age.[131] Bactericidal titres increased 50- to 60-fold from the initial levels, i.e. these vaccines mimic Hib conjugates in their ability to prime infants immunologically. The duration of any long term immunity they may induce remains to be seen, but 3 doses of MenC conjugate at 2, 3 and 4 months showed persistent bactericidal activity and, thus, probable evidence of immunological memory for at least 1 year after.[132]

MenA + C conjugate was tested also in the Gambia. Interestingly enough, MenA polysaccharide antibodies increased progressively with 1, 2 or 3 doses, whereas a single dose of MenC conjugate at 6 months elicited a greater response than 2 doses at age 2 and 6 months (mean titres 2285 *vs* 1370, respectively; $p < 0.001$).[130] However, those vaccinated 3 times showed greater concentrations (mean titre 2760) than those vaccinated twice, raising the possibility that this hyporesponsiveness can be overcome with increasing doses (not amount of antigen[47]).

When the same children received a further dose of MenA + C conjugate or plain polysaccharides (control group), another surprising observation was made:[133] MenC conjugate induced immunological memory, as demonstrated by both ELISA and bactericidal assays, whereas no evidence for this was observed with MenA, regardless of whether conjugate or polysaccharide was used. The reason remains open to interpretation. In Niger, a study was carried out with MenA + C diphtheria-toxoid conjugate in infants.[134] A larger (16μg) dose of antigen proved better than smaller ones (4 or 1μg) in terms of the geometric mean titres of bactericidal activity; with the largest dose levels of 370 and 325 for MenA and MenC were achieved, respectively. Traditional MenA + C polysaccharide induced titres at 7.4 and 30.2, respectively. It is probably only a question of time until meningococcal conjugates take the place of polysaccharides.

Except for local tenderness in 30 to 75% of those vaccinated,[128,131] no conjugates evaluated to date have been associated with significant adverse effects attributable to vaccines. Reactogenicity seems not to be dependent on the dose used.[134]

5.2 MenB

Development of MenB conjugates has also been hit by snags. When MenB polysaccharide was conjugated to tetanus toxoid or CRM_{197} protein[135] (both used successfully in Hib vaccines), good seroresponse was elicited in mice, but most antibodies were not directed against MenB but an epitope between the spacer and polysaccharide or carrier. However, specific bactericidal antibodies were also elicited, though in low titres. It remains to be seen if this track can be followed further since it raises the old question of the potential risks of inducing an autoimmune response.[24]

Another approach has been to conjugate chemically modified propionylated polysialic acid from *E. coli* K1 polysaccharide directly to tetanus toxoid and recombinant MenB porin.[136] Good bactericidal activity was elicited in baboons and Rhesus monkeys. Since the activity was completely inhibited by free *N*-propionylated polysaccharide, the immunopotentiating ability of Neisseria porins could be regenerated from a recombinantly produced molecule. No adverse effects were observed.

5.3 MenA + B + C

The final goal is, of course, to combine all important serogroups in the one vaccine. One laboratory which has already conjugated MenA and MenC polysaccharides to tetanus toxoid has joined that technology with the one in which modified MenB polysaccharide is conjugated to recombinant meningococcal B class 3 outer membrane protein.[137] The first experiments in mice show this trivalent conjugate is as immunogenic as the monovalent controls and, moreover, bactericidal antibodies are elicited against all 3 components without significant interference.

6. When to Use Meningococcal Vaccines

Avid discussion is ongoing regarding the indications for vaccine use,[138,139,140] and authoritative recommendations do exist.[4,141,142] The question is easily answered if an epidemic strikes a region and a group-specific vaccine is available (although we may query whether MenC polysaccharide should[94] or should not[56] be used in infants). The problems arise especially in 2 situations: what to do with only a cluster of cases,[2,3] and when the slowly increasing incidence should trigger routine vaccinations, at least in some populations. Table IV summarises the views of the author: regardless of serogroup, immediate chemoprophylaxis[141] should be initiated in all cases, since one-third of secondary cases develop within 2 days.[146]

6.1 Non-Outbreak Conditions

The incidence is so low in most countries and age groups – 1 to 5 cases per 100 000 population per year – that there is no reason for routine vaccinations, except among the well defined risk groups (table IV).[7,141] When endemic disease increases to ‘hyperendemic’ is a matter of definition, and depends on available resources whether costly, large-scale vaccination programmes should be launched.

6.2 Outbreak Conditions

Because of the problems with definition of an outbreak (or epidemic), various criteria have been used in vaccination campaigns. In the US, an attack rate (expressed for MenC)[142] exceeding 10 cases per 100 000 per 3 months – (number of cases during a 3-month period/number of population at risk) × 100 000 - has been proposed for consideration of vaccination in a large setting or population. Since, in closed-group settings such as a school, this definition would be fulfilled too easily, an attack rate exceeding 1/1000 with at least 3 confirmed cases (of MenA or MenC disease) within weeks[88] seems a better criterion there. In Canada, a campaign against a rather lethal MenC disease was launched when the annual incidence of 5 per 100 000 at ages

Table IV. Indications for the use of various meningococcal vaccines, provided the serogroup is confirmed as one of those in the vaccine

Non-outbreak conditions
[A + C or A + C + W135 + Y polysaccharides or MenC (or MenA) conjugates]
Generally no reason for routine vaccinations[a]
Risk groups
military recruits
close contacts of index case
pilgrims to Saudi Arabia (Hajj)
underlying disease
terminal complement deficiency
asplenia
alcoholics
travelling to risk area
Outbreak conditions
[polysaccharide or conjugate vaccines]
Close contacts (see text)
If attack rate exceeds 10 cases/100 000 population per 3mo[142]
≥2 cases in same classroom, day care centre, etc.
Attack rate > 1/1000 with ≥3 cases in closed-group setting
Epidemic conditions
[polysaccharide or conjugate vaccines, or the outer membrane MenB vaccines]
Threshold of 15 cases/100 000 population in 1wk exceeded for 2 consecutive weeks[4,140]
Steadily increasing incidence
Shift in age distribution towards older groups[8,143-145]

a Depends on incidence and resources.

1 to 20 years was reached in 2 consecutive years.[14] In Spain, a tighter criterion is suggested: ≥10 per 100 000 per year at all ages.[147] The WHO guidelines mainly for the African meningitis belt[28] recommend vaccination if a *weekly* incidence exceeds 15 per 100 000 for 2 consecutive weeks.

Complicated definitions have been formulated for ‘close contacts’ of a meningococcal case, but the earlier version works in everyday practice: ‘individuals who frequently sleep and eat in the same dwelling with an index case’.[148] Hence, a schoolmate is not a close contact, not even if the students share the same classroom,[149] unless they sit close to each other.[88] However, the great emotion and anxiety generated by only one or two cases is sometimes most easily relieved by vaccination of classmates. Chemoprophylaxis in a school, etc., is recommended[146] immediately after the second case of the same serogroup.

Bivalent A + C or quadrivalent A + C + W_{135} + Y vaccine is usually available. This author believes that potential hyporesponsiveness to MenC component is not an issue.[94] Protection, even though incomplete, is sufficient to justify vaccination under epidemic conditions from 3 months of age onwards, perhaps with a booster about 3 months later, at least when dealing with MenA disease.[57] As for MenB disease, the Cuban vaccine is available in many countries, and should be used, preferably with 1 or 2 booster doses.

6.3 Epidemic Conditions

MenA (tables I) and MenC (table II) vaccinations have undoubtedly extinguished epidemics, regardless of whether a monovalent, bivalent or quadrivalent vaccine was used. A dose of vaccine may be given to children at age 3 months and above; a second dose about 3 months later might be beneficial up to at least 18 months of age,[57] though in MenC disease this is controversial.[47] Detection of an epidemic is difficult when reporting is slow and unreliable. A shift in the age distribution of (meningitis) cases from infants and small children towards those of school age suggests an impending epidemic.[8,143-145] An ‘alert threshold’ of 15 per 100 000 cases in 1 week for 2 consecutive weeks has been used in tropical Africa to suggest the onset of an epidemic.[140] In Finland, a MenA epidemic waned when those in the age group 3 months to 19 years were vaccinated.[83] Herd immunity, that also has been observed in MenC vaccination,[94] allows considerable savings, provided the target group is chosen successfully.

Children younger than 5 years should receive at least one more dose 1 to 3 years later. Older children and adults may benefit from repeated doses about 5 years apart, if the risk continues.[61,81] W_{135} and Y infections are too rare to provide any reliable data on vaccine efficacy, but it may be expected to be as good as with MenA and MenC.[45,52] An interesting calculation was done recently in Burkina

Faso, the country with the highest incidence of reported meningococcal disease:[150] routine polysaccharide vaccination would prevent 26 or 33% of annual deaths with 1 or 3 doses, respectively, whereas an active vaccination campaign only once an epidemic has commenced would prevent 27%. The costs per death prevented would be $US1300, 1700 and 1200, respectively. An outbreak response seems financially the most feasible approach in the conditions of the meningitis belt.

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