

WHO Position Paper on Meningococcal vaccines

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Selected references

Epidemiology of meningococcal diseases

Tzeng YL, Stephens DS. Epidemiology and pathogenesis of *Neisseria meningitidis*. *Microbes Infect.* 2000 May;2(6):687-700.

Neisseria meningitidis, an exclusive pathogen of humans, remains the leading worldwide cause of meningitis and fatal sepsis, usually in otherwise healthy individuals. In recent years, significant advances have improved our understanding of the epidemiology and genetic basis of meningococcal disease and led to progress in the development of the next generation of meningococcal vaccines. This review summarizes current knowledge of the human susceptibility to and the epidemiology and molecular pathogenesis of meningococcal disease.

Moore PS. Meningococcal meningitis in sub-Saharan Africa: a model for the epidemic process. *Clin Infect Dis.* 1992 Feb;14(2):515-25.

Epidemic group A meningococcal meningitis follows a unique and distinctive pattern in sub-Saharan Africa. Advances in molecular and field epidemiology have begun to elucidate the mechanisms of meningococcal meningitis epidemics. Epidemics result from a complex combination of host, organism, and environmental risk factors. Recent studies suggest that "antigenic shifts" in group A meningococcal clones may trigger an outbreak of disease by suddenly decreasing herd immunity within a population. Although the introduction of new group A meningococcal strains into a susceptible population contributes to the likelihood of an epidemic, the presence of additional environmental factors, such as low humidity and coincident respiratory tract infections, are also necessary for an epidemic to occur. Despite the unique behavior of group A meningococcal disease in sub-Saharan Africa, the application of similar methods of epidemiological analysis may be useful for determining epidemic processes for other diseases.

Connolly M, Noah N. Is group C meningococcal disease increasing in Europe? A report of surveillance of meningococcal infection in Europe 1993-6. *European Meningitis Surveillance Group. Epidemiol Infect.* 1999 Feb;122(1):41-9.

A surveillance system to assess the impact and changing epidemiology of invasive meningococcal disease in Europe was set up in 1987. Since about 1991, contributors from national reference laboratories, national communicable disease surveillance centres and institutes of public health in 35 European countries provided information on all reported cases of meningococcal disease in their country. We describe some trends observed over the period 1993-6. The main findings were: the overall incidence of meningococcal disease was 1.1 per 100000 population but there was some evidence

of a slow increase over time and with northern European countries tending to have a higher incidence (Kendall correlation 0.5772, $P < 0.001$), an increasing predominance of serogroup C, and a shift in the age distribution towards teenagers and away from younger children (chi2 test for trend 44.56, $P < 0.0001$), although about half of the cases were under 5 years of age. The overall case fatality rate was 8.3% and the most common serosubtypes were B:15:P1.7,16 and C:2a:P1.2,5.

Campagne G, Schuchat A, Djibo S, Ousseini A, Cisse L, Chippaux JP. Epidemiology of bacterial meningitis in Niamey, Niger, 1981-96. Bull World Health Organ. 1999;77(6):499-508.

In the African meningitis belt the importance of endemic meningitis is not as well recognized as that of epidemics of meningococcal meningitis that occur from time to time. Using retrospective surveillance, we identified a total of 7078 cases of laboratory-diagnosed bacterial meningitis in Niamey, Niger, from 1981 to 1996. The majority (57.7%) were caused by *Neisseria meningitidis*, followed by *Streptococcus pneumoniae* (13.2%) and *Haemophilus influenzae b* (Hib) (9.5%). The mean annual incidence of bacterial meningitis was 101 per 100,000 population (70 per 100,000 during 11 non-epidemic years) and the average annual mortality rate was 17 deaths per 100,000. Over a 7-year period (including one major epidemic year) for which data were available, *S. pneumoniae* and Hib together caused more meningitis deaths than *N. meningitidis*. Meningitis cases were more common among males and occurred mostly during the dry season. Serogroup A caused 85.6% of meningococcal meningitis cases during the period investigated; three-quarters of these occurred among children aged < 15 years, and over 40% among under-5-year-olds. Both incidence and mortality rates were highest among infants aged < 1 year. In this age group, Hib was the leading cause of bacterial meningitis, followed by *S. pneumoniae*. The predominant cause of meningitis in persons aged 1-40 years was *N. meningitidis*. Use of the available vaccines against meningitis due to *N. meningitidis*, *S. pneumoniae*, and Hib could prevent substantial endemic illness and deaths in sub-Saharan Africa, and potentially prevent recurrent meningococcal epidemics.

PIP: The study presented information on the epidemiology of bacterial meningitis in Niamey, Niger from 1981 to 1996 using retrospective surveillance. During the 15-year period, 7078 cases of laboratory-diagnosed bacterial meningitis were identified. 3 years (1984-85, 1985-86, and 1994-95) were considered to be epidemic years, and in these years incidence of bacterial meningitis exceeded 140 cases/100,000 population. The major pathogens were *Neisseria meningitidis* (57.7%), *Streptococcus pneumoniae* (13.2%), and *Haemophilus influenzae* (Hib) (9.5%). Mean annual incidence of bacterial meningitis was 101/100,000 population with an average annual mortality rate of 17 deaths/100,000. Both *S. pneumoniae* and Hib had caused more meningitis deaths than *N. meningitidis*, as observed over the 7-year period for which data were available. Meanwhile, *N. meningitidis* was the major cause of meningitis in persons aged 1-40 years. Meningitis was more common among males than females and was more prevalent during dry seasons. Incidence of meningococcal meningitis was higher (74.3%) in children under 15 years of age, and over 40% of these cases occurred in children below 5 years old. Infants aged less than 1 year had the highest incidence and mortality rates; neonatal (1 month of age) meningitis was identified in 101 cases. The high rate of endemic illness and deaths due to meningitis in sub-Saharan Africa could

be prevented through the use of available vaccines such as meningococcal polysaccharide vaccines and Hib conjugate vaccines.

Ramsay M, Kaczmarski E, Rush M, Mallard R, Farrington P, White J. Changing patterns of case ascertainment and trends in meningococcal disease in England and Wales. Commun Dis Rep CDR Rev. 1997 Apr 4;7(4):R49-54.

We have reviewed data on meningococcal disease routinely collected in England and Wales from 1989 to 1995 to illustrate and explain changing patterns and guide future surveillance. Statutory notifications of meningococcal meningitis and septicaemia, laboratory confirmed infections, and death registrations coded as meningococcal disease were analysed in terms of their numbers, the age of cases, season of the report, and (if available) site of isolation, serogroup, and serotype. Case fatality rates were estimated for clinically diagnosed and culture confirmed cases. The number of cases notified each year, in particular those notified as septicaemia, rose significantly over the period ($p < 0.0001$) but there was no net change in the number of culture confirmed cases. Case fatality rates estimated from routine data fell, most markedly for cases notified as septicaemia, but the true case fatality rate of culture confirmed cases did not change between 1993 and 1995. These data suggest that reporting practice changed between 1989 and 1995 and that the ascertainment of clinically diagnosed disease improved, particularly for meningococcal septicaemia. Late in 1995, reports from all data sources increased and the age distribution of both notified and laboratory confirmed cases changed. These changes were accompanied by an increase in the proportion of infections due to *Neisseria meningitidis* of serogroup C and a significant increase in serotype C2a infections ($p < 0.0001$). Continuing efforts to reconcile data from several sources will be needed to ensure that routine data can be interpreted accurately to provide evidence for the development of future vaccination policy and to monitor vaccination programmes. In addition, the role of non-culture diagnosis will be crucial in enhancing surveillance based on clinical diagnoses.

Caugant DA, Froholm LO, Bovre K, Holten E, Frasch CE, Mocca LF, Zollinger WD, Selander RK. Intercontinental spread of a genetically distinctive complex of clones of *Neisseria meningitidis* causing epidemic disease. 1: Proc Natl Acad Sci U S A. 1986 Jul;83(13):4927-31.

Strains of *Neisseria meningitidis* responsible for an epidemic of meningococcal disease occurring in Norway since the mid-1970s and for recent increases in the incidence of disease in several other parts of Europe have been identified by multilocus enzyme electrophoresis as members of a distinctive group of 22 closely related clones (the ET-5 complex). Clones of this complex have also colonized South Africa, Chile, Cuba, and Florida, where they have been identified as the causative agents of recent outbreaks of meningococcal disease. There is strong circumstantial evidence that outbreaks of disease occurring in Miami in 1981 and 1982 were caused in large part by bacteria that reached Florida via human immigrants from Cuba.

Background on Mc vaccines and serological correlates of

protection

Rosenstein NE, Fischer M, Tappero JW. Meningococcal vaccines. Infect Dis Clin North Am. 2001 Mar;15(1):155-69.

Global control and prevention of meningococcal disease depends on the further development of vaccines that overcome the limitations of the current polysaccharide vaccines. Protein-polysaccharide conjugate vaccines likely will address the marginal protective antibody responses and short duration of immunity in young children derived from the A, C, Y, and W-135 capsular polysaccharides, but they will be expensive to produce and purchase, and may not offer a practical solution to the countries with greatest need. In addition, OMP vaccines have been tested extensively in humans and hold some promise in the development of a serogroup B vaccine, but are limited by the antigenic variability of these subcapsular antigens and the resulting strain-specific protection. Elimination of meningococcal disease likely will require a novel approach to vaccine development, ideally incorporating a safe and effective antigen or antigens common to all meningococcal serogroups. As a solely human pathogen, however, *N. meningitidis* has developed many tools with which to evade the human immune system, and likely will pose a formidable challenge for years to come.

Maslanka SE, Gheesling LL, Libutti DE, Donaldson KB, Harakeh HS, Dykes JK, Arhin FF, Devi SJ, Frasch CE, Huang JC, Kriz-Kuzemenska P, Lemmon RD, Lorange M, Peeters CC, Quataert S, Tai JY, Carlone GM. Standardization and a multilaboratory comparison of *Neisseria meningitidis* serogroup A and C serum bactericidal assays. The Multilaboratory Study Group. Clin Diagn Lab Immunol. 1997 Mar;4(2):156-67.

A standardized serum bactericidal assay (SBA) is required to evaluate the functional activity of antibody produced in response to *Neisseria meningitidis* serogroup A and C vaccines. We evaluated assay parameters (assay buffer, target strains, growth of target cells, target cell number, complement source and concentration, and methods for growth of surviving bacteria) which may affect the reproducibility of SBA titers. The various assay parameters and specificity of anticapsular antibody to five serogroup A strains (A1, ATCC 13077, F8238, F9205, and F7485) and four serogroup C strains (C11, G7880, G8050, and 1002-90) were evaluated with Centers for Disease Control and Prevention meningococcal quality control sera. The critical assay parameters for the reproducible measurement of SBA titers were found to include the target strain, assay incubation time, and complement. The resulting standardized SBA was used by 10 laboratories to measure functional anticapsular antibody against serogroup A strains F8238 and serogroup C strain C11. In the multilaboratory study, SBA titers were measured in duplicate for 14 pairs of sera (seven adults and seven children) before and after immunization with a quadrivalent polysaccharide (A, C, Y, and W-135) vaccine. The standardized SBA was reliable in all laboratories regardless of experience in performing SBAs. For most sera, intralaboratory reproducibility was ± 1 dilution; interlaboratory reproducibility was ± 2 dilutions. The correlation between median titers (interlaboratory) and enzyme-linked immunosorbent assay total antibody concentrations was high for both serogroup A ($r = 0.86$; $P < 0.001$; slope = 0.5) and serogroup C ($r = 0.86$; $P < 0.001$; slope = 0.7). The specified assay, which includes

the critical parameters of target strain, incubation time, and complement source, will facilitate interlaboratory comparisons of the functional antibody produced in response to current or developing serogroup A and C meningococcal vaccines.

Polysaccharide vaccines (Mc groups A and C-vaccines)

Peltola H, Makela H, Kayhty H, Jousimies H, Herva E, Hallstrom K, Sivonen A, Renkonen OV, Pettay O, Karanko V, Ahvonen P, Sarna S.

Clinical efficacy of meningococcus group A capsular polysaccharide vaccine in children three months to five years of age. N Engl J Med. 1977 Sep 29;297(13):686-91.

We performed field trials in the course of an epidemic in Finland to learn whether Group A meningococcal capsular polysaccharide vaccine protects infants and young children from meningitis. The first trial involved 130,178 children between the ages of three months and five years; 49,295 children received the vaccine, 48,977 received a control Haemophilus influenzae Type b polysaccharide vaccine, and 31,906 remained unvaccinated. No cases of meningitis or sepsis caused by Group A meningococci were seen in the first year of observation among the children vaccinated with meningococcal vaccine whereas six occurred among those vaccinated with the H. influenzae vaccine and 13 among those not vaccinated. In the second trial 21,007 children of the same ages received the meningococcal vaccine. No cases caused by Group A occurred among those vaccinated, although five to seven would have been expected within the year. Meningococcal Group A vaccine appears efficacious in young infants and children.

Kayhty H, Karanko V, Peltola H, Sarna S, Makela PH. Serum antibodies to capsular polysaccharide vaccine of group A Neissera meningitidis followed for three years in infants and children. J Infect Dis. 1980 Dec;142(6):861-8.

The persistence of antibodies to the capsular polysaccharide of group A Neissera meningitidis was studied in 2,030 persons vaccinated at the age of 10 weeks to 19 years and followed for three years. Both the initial antibody response and the persistence of elevated serum titers of antibody were markedly age-dependent. In infants younger than 12 months, a statistically significant antibody response was obtained after a booster dose of vaccine and was maintained for one year. In infants aged 12-17 months, the response after booster vaccination was higher and was maintained for two years. Children older than 17 months did not receive a booster injection. The initial response in the age group 18-23 months was good, but the decline of antibody level was more rapid, so that an elevated antibody titer was not maintained for more than one year. With increasing age, the decrease of the vaccination-induced antibody levels was progressively slower throughout the age bracket studied.

Reingold AL, Broome CV, Hightower AW, Ajello GW, Bolan GA, Adamsbaum C, Jones EE, Phillips C, Tiendrebeogo H, Yada A. Age-specific differences in

duration of clinical protection after vaccination with meningococcal polysaccharide A vaccine. Lancet. 1985 Jul 20;2(8447):114-8.

Sequential case-control studies were used to monitor changes in the clinical protection induced by group A meningococcal polysaccharide vaccine over a 3-year period. Overall, vaccine efficacy declined from 87% 1 year after vaccination to 70% and 54% at 2 and 3 years, respectively. When stratified by age at time of vaccination the data showed that, although vaccine efficacy remained high in children greater than or equal to 4 years of age (vaccine efficacy 85%, 74%, and 67% at 1, 2, and 3 years after vaccination, respectively), it declined dramatically in those less than 4 years of age at time of vaccination (vaccine efficacy 100%, 52%, and 8%, respectively, at 1, 2, and 3 years after vaccination). Thus, a single dose of group A meningococcal vaccine does not yield lasting clinical protection in children less than 4 years of age.

Lennon D, Gellin B, Hood D, Voss L, Heffernan H, Thakur S. Successful intervention in a group A meningococcal outbreak in Auckland, New Zealand. Pediatr Infect Dis J. 1992 Aug;11(8):617-23

During two consecutive winter seasons (1985 and 1986) Auckland, New Zealand, experienced epidemic rates of Group A meningococcal disease, a pattern not previously recognized in New Zealand. The overall rate was 8.3/100,000/year. The highest annual rate (64.7) occurred in children 0 to 23 months of age. A city-wide vaccine campaign commencing in May, 1987, was conducted over 6 weeks among children 3 months to 13 years of age with special emphasis on reaching populations at highest risk (Maori and Pacific Island Polynesian children in certain geographic regions of Auckland). Children from 2 to 13 years of age received a single dose of monovalent Group A meningococcal vaccine. Children ages 3 to 23 months received two doses at least 1 month apart. Overall approximately 130,000 doses were delivered; coverage was approximately 90% in the single dose target group. Among the younger children approximately 89% received the primary dose. Only approximately 26% received the recommended "booster" dose. After 2 1/2 years of active surveillance (1987 to 1989) there were no cases of invasive Group A meningococcal disease in children appropriately vaccinated for age. In contrast to this 100% efficacy the efficacy of a single dose of monovalent Group A meningococcal vaccine to prevent illness in the youngest children during the 1987 epidemic period was 52% (95% confidence interval (-330%, 95%)) falling to 16% (95% confidence interval, (-538%, 90%)) after 1 year. Four cases that occurred in infants 3 to 7 weeks before the scheduled "booster" campaign supports limited true efficacy. However, the prescribed 1 to 3-month interval between the two doses in infants may be too long.(ABSTRACT TRUNCATED AT 250 WORDS)

Woods CW, Armstrong G, Sackey SO, Tetteh C, Bugri S, Perkins BA, Rosenstein NE. Emergency vaccination against epidemic meningitis in Ghana: implications for the control of meningococcal disease in West Africa. Lancet. 2000 Jan 1;355(9197):30-3.

BACKGROUND: Recurrent epidemics of meningococcal disease have been reported

throughout the African meningitis belt since description of the disease in 1912. Meningococcal polysaccharide vaccines can effectively prevent disease but the optimum strategy for their use in this setting has been controversial. We used data from an outbreak of meningococcal disease in northern Ghana in 1997 to assess the potential effect of different vaccination strategies. **METHODS:** We identified all reported cases of meningococcal meningitis and estimated the number of cases and deaths that could have been prevented by vaccination through use of a simple mathematical model. We then assessed the potential effect of different vaccination strategies and the burden of these strategies on the public-health system. **FINDINGS:** In the three affected regions in northern Ghana there were 18703 cases and 1356 deaths reported between November, 1996, and May, 1997. Vaccination began in the third week of February and continued to April, reaching 72% of the at-risk population and preventing an estimated 23% of cases and 18% of deaths. A strategy of routine childhood and adult immunisation would have prevented 61% of cases had this same rate of vaccine coverage been achieved and maintained before the epidemic. If vaccination had started after the onset of the epidemic in January, as currently advocated by WHO guidelines, a similar proportion (61%) of cases could have been prevented. **INTERPRETATION:** Prevention of epidemics of meningococcal disease in west Africa will be difficult until long-lasting conjugate vaccines capable of interrupting transmission of *Neisseria meningitidis* can be incorporated into routine infant-immunisation schedules. Until then, the strategy of surveillance and response advocated by WHO is as effective and more practical than a strategy of routine childhood and adult vaccination with currently available polysaccharide vaccines.

PIP: This study assessed the potential effects of different vaccination strategies using data from the 1997 meningococcal outbreak in northern Ghana. Since the description of the disease in 1912, recurrent epidemics of meningococcal disease have been reported throughout the African meningitis belt. The use of meningococcal polysaccharide vaccines has been proven to effectively prevent the disease, although the method of vaccine distribution was disputable. Using a simple mathematical model, meningococcal meningitis cases and deaths, which could have been forestalled by vaccination, were identified, and the effect of developed vaccination strategies on the public health system was analyzed. About 18,703 cases and 1356 deaths were reported in 3 regions of northern Ghana between November 1996 and May 1997. Vaccination was conducted between February and April, which covered 72% of the high-risk population and prevented approximately 23% of cases and 18% of deaths. Routine childhood and adult immunization would have prevented 61% of cases had this same rate of vaccine coverage been achieved and maintained before the epidemic. This study suggests that the prevention of the meningococcal disease epidemic in West Africa would be difficult unless long-lasting conjugate vaccines are incorporated into routine infant immunization schedules. For now, the surveillance and response strategies advocated by the WHO serve as an effective and practical intervention.

Robbins JB, Towne DW, Gotschlich EC, Schneerson R. "Love's labours lost": failure to implement mass vaccination against group A meningococcal meningitis in sub-Saharan Africa. Lancet. 1997 Sep 20;350(9081):880-2.

PIP: Despite the availability of a safe, effective polysaccharide vaccine, group A meningococcal meningitis epidemics persist in sub-Saharan Africa. In October 1996,

there were almost 150,000 reported cases and 15,000 deaths, the majority of which involved children. At 3 months of age, induction of protective group A meningococcal antibody levels requires 2 injections at least 1 month apart. Reinjection of 5-year-old children increases group A antibodies to long-term protective levels. During meningitis epidemics in Nigeria, Mali, and Rwanda, fatality was significantly reduced in areas where scarce vaccine was administered selectively. Although effective on an individual basis, selective vaccination is unable to control meningitis epidemics. In Chad, mass vaccination of the entire population (excluding infants under 12 months) eliminated the disease. Successful mass vaccination against group A meningococcal epidemics also has been reported in Saudi Arabia, China, and refugee camps in Africa. Although cost is cited as an obstacle to routine mass vaccination to prevent meningococcal meningitis in South Africa, prevention is the least expensive approach to disease control. It is recommended that the entire population of Africa's meningitis belt receive group A meningococcal vaccine in accordance with the recommended age schedule in a mass vaccination program.

Miller MA, Wenger J, Rosenstein N, Perkins B. Evaluation of meningococcal meningitis vaccination strategies for the meningitis belt in Africa. *Pediatr Infect Dis J.* 1999 Dec;18(12):1051-9.

BACKGROUND: Although the meningococcal polysaccharide vaccine has contributed to the control of Group A meningitis in the "meningitis belt" of Africa, recurrent large outbreaks have led to questions regarding vaccination strategy. We evaluated current and hypothetical vaccination strategies for the region. **METHODS:** A model was formulated to analyze the effectiveness and costs of vaccine campaigns in response to outbreaks based on 7 years of weekly incidence data from Burkina Faso. Additional models analyzed the potential impact and costs of either a 1- or 4-dose routine scheduled delivery of meningococcal polysaccharide vaccine based on data reported to the World Health Organization from 16 countries during 1948 through 1996. Vaccine efficacy, vaccination coverage and economic data from literature reviews provided model assumptions. **RESULTS:** For Burkina Faso neither 1- nor 4-dose vaccination schedules would prevent >30% of meningitis cases compared with the 42% prevented through an outbreak response program of vaccinating districts, which reach an incidence of 15 per 100,000 persons for 2 weeks. For the entire meningitis belt, routine coverage with the 1- or 4-dose schedule meningococcal vaccine would require 4.9 and 19.6 million doses annually, respectively, for an annual net cost of \$4.4 to \$12.3 million and prevent an average 10,300 to 12,600 cases (23 to 28%), assuming a long term vaccine efficacy of 50%. In addition an initial "catch-up" campaign costing up to \$72 million to vaccinate the population from 1 to 30 years of age would be required before achieving that level of effectiveness. **CONCLUSION:** Given the relatively poor routine vaccination coverage in this region, current strategies of vaccination campaigns that achieve higher coverage would generally be more effective and less costly than the modeled routine scheduled programs, assuming that campaigns can be rapidly implemented. Until a better vaccine is available, countries in this region would be more efficient in improving the response times to outbreaks, perhaps through improved surveillance, and in bolstering existing vaccination infrastructures rather than embarking on strategies of questionable effectiveness.

Outer membrane protein vaccines. (Mc group B vaccines)

Bjune G, Hoiby EA, Gronnesby JK, Arnesen O, Fredriksen JH, Halstensen A, Holten E, Lindbak AK, Nokleby H, Rosenqvist E, et al. Effect of outer membrane vesicle vaccine against group B meningococcal disease in Norway. Lancet. 1991 Nov 2;338(8775):1093-6

For more than 15 years, Norway has had the highest incidence of meningococcal disease in northern Europe, with 80% of cases being due to serogroup B meningococci. The case-fatality has remained high, at about 10%. In this study, an outer membrane vaccine, which had previously been shown to induce an increase in bactericidal antibodies to the parent strain, was assessed in a large-scale, randomised, double-blind trial. From October, 1988, 171,800 students in secondary schools volunteered to take part in a double-blind, placebo-controlled, efficacy trial with school as the randomisation unit. Hospitals and clinics that routinely receive patients with infectious disease were asked to report urgently all cases of suspected meningitis and/or septicaemia in 13-21-year-old students in Norway. These cases were registered and further investigated according to a detailed protocol. 89 out of the 221 cases investigated by June 3, 1991, were shown to be severe systemic disease due to group B meningococci. 36 cases in 35 schools took part in the trial (11 schools with vaccinated students and 24 with students given placebo). The calculated rate of protection was thus 57.2% ($p = 0.012$, one-sided test). The findings suggest that, although the vaccine conferred protection against group B meningococcal disease, the effect was insufficient to justify a public vaccination programme.

de Moraes JC, Perkins BA, Camargo MC, Hidalgo NT, Barbosa HA, Sacchi CT, Landgraf IM, Gattas VL, Vasconcelos Hde G, et al. Protective efficacy of a serogroup B meningococcal vaccine in Sao Paulo, Brazil. Lancet. 1992 Oct 31;340(8827):1074-8.

Serogroup B *Neisseria meningitidis* is the most common cause of epidemic meningococcal disease in developed countries. Until recently no vaccine has been available for prevention of infection with this organism. In an attempt to control epidemic serogroup B meningococcal disease in greater Sao Paulo, Brazil, during 1989 and 1990, a Cuban-produced outer-membrane-protein-based serogroup B meningococcal vaccine was given to about 2.4 million children aged from 3 months to 6 years. We have done a case-control study to estimate the efficacy of the vaccine in greater Sao Paulo. Microbiologically confirmed cases of serogroup B meningococcal disease were identified through hospital-based surveillance. Controls were matched by neighbourhood and age. Vaccination status was confirmed by inspection of vaccination cards. Between June, 1990, and June, 1991, 112 patients and 409 matched controls with confirmed vaccine status were enrolled. Estimated vaccine efficacy varied by age: 48 months or older = 74% (95% CI 16 to 92%), 24 to 47 months = 47% (-72 to 84%), and less than 24 months = -37% (< -100 to 73%). Our results suggest that the Cuban-produced vaccine may be effective for prevention of serogroup B meningococcal disease in older children and adults.

Conjugate vaccines (Mc groups A and C vaccines)

Twumasi PA Jr, Kumah S, Leach A, O'Dempsey TJ, Ceesay SJ, Todd J, Broome CV, Carlone GM, Pais LB, Holder PK, et al. A trial of a group A plus group C meningococcal polysaccharide-protein conjugate vaccine in African infants. J Infect Dis. 1995 Mar;171(3):632-8.

The safety and immunogenicity of a group A plus group C meningococcal polysaccharide-CRM197 conjugate vaccine was evaluated in 304 8- to 10-week-old Gambian infants. Infants were immunized with one, two, or three doses of conjugate vaccine or with two doses of a meningococcal A plus C polysaccharide vaccine. The conjugate vaccine produced few systemic side effects, and local reactions were similar to those produced by the polysaccharide vaccine. Postvaccination group A meningococcal polysaccharide antibody levels, measured by ELISA, increased progressively after one, two, or three doses of conjugate vaccine. However, one dose of conjugate vaccine given at the age of 6 months induced a higher group C meningococcal antibody response than did two doses of conjugate vaccine given at 2 and 6 months. Two doses of conjugate vaccine induced higher levels of antibody than did two doses of polysaccharide vaccine. Thus, this new meningococcal conjugate vaccine proved to be safe and immunogenic.

Lieberman JM, Chiu SS, Wong VK, Partidge S, Chang SJ, Chiu CY, Gheesling LL, Carlone GM, Ward JI. Safety and immunogenicity of a serogroups A/C Neisseria meningitidis oligosaccharide-protein conjugate vaccine in young children. A randomized controlled trial. JAMA. 1996 May 15;275(19):1499-503.

OBJECTIVE: To assess the safety and immunogenicity of a bivalent serogroups A/C meningococcal oligosaccharide-protein conjugate vaccine compared with the licensed meningococcal polysaccharide vaccine. **DESIGN:** Randomized controlled trial. **STUDY POPULATION:** Ninety healthy 18- to 24-month-old children who were seen at a southern California Kaiser Permanente clinic. **INTERVENTIONS:** Vaccination with either the meningococcal conjugate vaccine (at 1 of 2 dosages) or the polysaccharide vaccine, with 2 doses given 2 months apart. **MAIN OUTCOME MEASUREMENTS:** Immune response to each vaccine dose as determined by measurement of serogroup-specific total antibodies by enzyme-linked immunosorbent assay (ELISA) and by assessment of serum bactericidal activity. **RESULTS:** Both vaccines appeared to be safe, and nearly all children responded with greater than 4-fold increases in antibody levels. The 2 dosages of the conjugate vaccine induced similar antibody responses; therefore, the data for the 2 conjugate vaccine groups were combined. Following 2 doses, ELISA antibody levels against group C meningococcus were significantly higher in conjugate vaccine recipients than in polysaccharide vaccine recipients (16.66 microg/mL vs. 8.31 microg/mL; $P < .001$), but antibody levels against group A were not significantly different (22.75 microg/mL vs 21.24 microg/mL; $P = .70$). The serum bactericidal assays showed striking differences between the conjugate and polysaccharide vaccine groups. Geometric mean serum bactericidal titers were significantly higher in conjugate vaccine recipients (755.6 vs

37.6 for group A, $P < .001$; 3197.9 vs 11.4 for group C, $P < .001$). **CONCLUSIONS:** The immune response induced by this meningococcal oligosaccharide-protein conjugate vaccine was qualitatively different from that induced by the polysaccharide vaccine, and the antibodies it elicited provided greater functional activity.

Fairley CK, Begg N, Borrow R, Fox AJ, Jones DM, Cartwright K. Conjugate meningococcal serogroup A and C vaccine: reactogenicity and immunogenicity in United Kingdom infants. *J Infect Dis.* 1996 Dec;174(6):1360-3.

The reactogenicity and immunogenicity of a serogroup A and C meningococcal polysaccharide-CRM197 conjugate vaccine was evaluated in 58 infants who received three doses at 2, 3, and 4 months of age. The conjugate vaccine produced few systemic side effects, and local reactions were significantly less common than those produced by the routine vaccinations. The prevaccination geometric mean titers (GMTs) of A and C polysaccharide antibodies were, respectively, 2.8 and 0.6 microg/mL, rising to 21.5 and 38.5 microg/mL by 1 month after the third dose (age 5 months) and falling to 3.1 and 2.2 microg/mL by 14 months of age. Prevaccination serum bactericidal titers against 2 serogroup C meningococci strains were $< 1/4$ in 49 of 52 infants, rising to a GMT of 1/3082 at 1 month after the third dose and falling by age 14 months to a GMT of 1/10. Thus, this meningococcal conjugate vaccine proved to be safe and immunogenic, inducing high levels of anti-C polysaccharide antibodies that were bactericidal in young infants.

PIP: In 1990, researchers compared data on 112 3 month-6 year old children who received a Cuban produced, outer-membrane-protein-based serogroup B meningococcal vaccine (cases) and lived in greater Sao Paulo, Brazil with data on 409 age and neighborhood matched controls to determine the protective efficacy of the vaccine against serogroup B meningococcal disease (*Neisseria meningitidis*). Health workers began administering the vaccine in 1989 to control an epidemic of serogroup B meningococcal disease in the area. In fact, in mid-1989 and early 1990, the rates of serogroup B meningococcal disease in 1-6 year old children in Sao Paulo were 2.07/100,000 and 2.3/100,000, respectively. Even though only 44% of serogroup B meningococcal isolates corresponded with the vaccine type strain (B:4:P1:15), many isolates had many of the same serotype or subtype antigens as the vaccine type strain. Thus the vaccine was able to protect against some other serogroup B meningococcal strains other than the vaccine type strain. Vaccine efficacy for 4-year old children was 74%, but was much lower for 24-47 month old children (47%) and 24-month old children (-37%). The change in the log odds ratio for vaccination by age was linear and significant ($p = .057$). The researchers suggested that poor vaccine efficacy among younger children may reflect a need for more boosting to achieve protective levels of immunity. The results showed that the Cuban-produced vaccine could contribute to control of outbreaks of serogroup B meningococcal disease by protecting older children and adults from the disease. Researchers need to conduct additional studies of the vaccine and other possible serogroup B meningococcal vaccines.

Anderson EL, Bowers T, Mink CM, Kennedy DJ, Belshe RB, Harakeh H, Pais L, Holder P, Carlone GM. Safety and immunogenicity of meningococcal A and C polysaccharide conjugate vaccine in adults. *Infect Immun.* 1994 Aug;62(8):3391-5.

A meningococcal vaccine containing group A and C polysaccharides conjugated to CRM197 was evaluated in 50 adults. Vaccinees were entered into one of five groups: 30 adults received a single dose of either 22, 11, or 5.5 micrograms of the conjugated A-C vaccine; 10 received an approved meningococcal vaccine; and 10 received saline injections. Local and systemic reactions to vaccines were recorded, and immune responses were determined. The experimental meningococcal vaccine was well tolerated, with the most frequent reaction being pain at the injection site. Both A and C polysaccharide components of the experimental vaccine were highly immunogenic, and total antibody concentrations 1 month postvaccination were not significantly different from the mean antibody concentrations among adults given the approved meningococcal vaccine. In addition, significant rises in immunoglobulin G, A, and M antibodies to both A and C polysaccharides occurred. Antibody concentrations measured at 6 and 12 months postvaccination had declined but remained significantly higher than prevaccination concentrations. Postvaccination meningococcal group C functional antibody activity increased more than 600-fold for both the polysaccharide and the conjugate vaccines. Further studies of this conjugated meningococcal vaccine are indicated for young children and infants.

MacDonald NE, Halperin SA, Law BJ, Forrest B, Danzig LE, Granoff DM. Induction of immunologic memory by conjugated vs plain meningococcal C polysaccharide vaccine in toddlers: a randomized controlled trial. JAMA. 1998 Nov 18;280(19):1685-9.

CONTEXT: Meningococcal polysaccharide vaccines are not used routinely in infants and toddlers, the groups at highest risk of invasive disease, because of poor immunologic responses to the *Neisseria meningitidis* serogroup C polysaccharide in these age groups. Meningococcal C conjugate vaccines offer the prospect of circumventing this problem. **OBJECTIVE:** To assess the immunogenicity and the induction of immunologic memory in toddlers by meningococcal C conjugate vaccine. **DESIGN:** A multicenter, randomized, observer-blinded controlled trial. **SETTING:** Urban and suburban family medicine or pediatric practices. **PARTICIPANTS:** Two hundred eleven healthy toddlers aged 15 to 23 months. **INTERVENTION:** Two injections at 2 months apart of meningococcal C conjugate (group 1, n = 69), plain meningococcal polysaccharide (group 2, n = 72), or hepatitis B virus vaccine (group 3, n = 70). All toddlers received a follow-up dose of plain meningococcal polysaccharide vaccine 12 months later. **MAIN OUTCOME MEASURES:** IgG meningococcal C anticapsular antibody concentrations determined by enzyme-linked immunosorbent assay and complement-mediated bactericidal antibody. **RESULTS:** In group 1, the magnitude of the IgG response to meningococcal C conjugate vaccine was more than 4-fold higher after dose 1 and more than 10-fold higher after dose 2 compared with meningococcal polysaccharide vaccine (group 2) (P<.001). Higher titers persisted in the meningococcal C conjugate group for at least 12 months (P<.001). Group 1, primed with meningococcal C conjugate, had 25-fold higher IgG responses to the meningococcal polysaccharide 1-year booster dose than the controls who had received hepatitis B virus vaccine initially and were given meningococcal polysaccharide vaccine 1 year later for the first time (P<.001). In contrast, group 2, primed with meningococcal polysaccharide, had a 2-fold lower response to the 1-year booster meningococcal polysaccharide dose than the hepatitis B virus control group (P = .006). Serum bactericidal responses paralleled the enzyme-linked immunosorbent

assay responses. **CONCLUSIONS:** Immunization of toddlers with meningococcal C conjugate vaccine induces high titers of anticapsular and bactericidal antibody. Furthermore, this vaccine induces immunologic memory to meningococcal C polysaccharide. In contrast, meningococcal polysaccharide vaccine is less immunogenic than the conjugate vaccine and also induces a hyporesponsive state that persists for at least 12 months.

MacLennan JM, Shackley F, Heath PT, Deeks JJ, Flamank C, Herbert M, Griffiths H, Hatzmann E, Goilav C, Moxon ER. Safety, immunogenicity, and induction of immunologic memory by a serogroup C meningococcal conjugate vaccine in infants: A randomized controlled trial. JAMA. 2000 Jun 7;283(21):2795-801.

CONTEXT: *Neisseria meningitidis* is a common cause of meningitis and septicemia in infants worldwide. Whether a meningococcal C conjugate vaccine protects infants against the serogroup C strain is unknown. **OBJECTIVES:** To determine whether a meningococcal C conjugate vaccine is safe and immunogenic and induces immunologic memory in infants. **DESIGN:** Single-center, double-blind, randomized controlled trial in 1995 and 1996. **SETTING:** Community, Oxfordshire, England. **PARTICIPANTS:** One hundred eighty-two healthy infants. **INTERVENTIONS:** Participants were randomly assigned to receive vaccination with 0.5-mL doses of 1 of 2 lots of meningococcal C conjugate vaccine (groups 1 and 2; n=60 in each group) or a hepatitis B control vaccine (group 3; n=62), administered with routine immunizations at 2, 3, and 4 months of age. Approximately half of each group received meningococcal C conjugate vaccine and half received plain meningococcal polysaccharide vaccine (MPS) at 12 months of age. **MAIN OUTCOME MEASURES:** Serum antibodies to meningococcal C polysaccharide, assayed by enzyme-linked immunosorbent assay, and serum bactericidal activity (SBA), at 2, 3, 4, 5, 12, and 13 months of age; local and systemic reactions, recorded for 6 days after each vaccination, compared by intervention group. **RESULTS:** Meningococcal C conjugate vaccine was well tolerated. After 3 doses, children in groups 1 and 2 achieved significantly higher meningococcal C IgG geometric mean concentrations (21 and 17 U/mL, respectively, vs 0.20 U/mL; P<.001) and SBA titers (629 and 420, respectively, vs 4.1; P<.001) than controls. At 12 months, antibody concentrations had decreased in all groups but remained significantly higher in children vaccinated with meningococcal C conjugate vaccine (SBA, 24 and 16 in groups 1 and 2, respectively, vs 4.2 in group 3; P<.001). Following vaccination with MPS at 12 months of age, SBA in the meningococcal C conjugate vaccine group was significantly higher than in controls (SBA, 789 vs 4.5; P<.001). **CONCLUSIONS:** Our data indicate that meningococcal C conjugate vaccine is safe and immunogenic and results in immunologic memory when given with other routinely administered vaccines to infants at 2, 3, and 4 months of age. *JAMA*. 2000;283:2795-2801

De Wals P, De Serres G, Niyonsenga T. Effectiveness of a mass immunization campaign against serogroup C meningococcal disease in Quebec. JAMA. 2001 Jan 10;285(2):177-81.

CONTEXT: An outbreak of meningococcal disease in Quebec province prompted a mass immunization program. The impact of this campaign on the epidemiology of meningococcal disease has not been studied. **OBJECTIVES:** To study the impact of a mass immunization campaign using polysaccharide vaccine on the epidemiology of meningococcal disease (MCD) and to assess serogroup C vaccine effectiveness (VE). **DESIGN, SETTING, AND SUBJECTS:** Analysis of MCD cases reported in Quebec from 1990 to 1998, before and after the mass immunization campaign was conducted during the winter of 1992-1993, when 84% of residents aged 6 months to 20 years (the target population, approximately 1.9 million individuals) were vaccinated. **MAIN OUTCOME MEASURES:** Incidence of MCD in 1990-1998; incidence of culture-proven serogroup C MCD between April 1, 1993, and March 31, 1998, compared among vaccinated and unvaccinated persons in the target population. **RESULTS:** The incidence of serogroup C disease decreased after the mass immunization campaign, from 1.4 per 100 000 in 1990-1992 to 0.3 per 100 000 in 1993-1998, and the overall incidence of other serogroups remained stable at 0.7 per 100 000, with a small increase in the proportion of cases caused by serogroup Y ($P = .009$). Protection from serogroup C MCD was indicated in the first 2 years after vaccine administration (VE, 65%; 95% confidence interval [CI], 20%-84%), but not in the next 3 years (VE, 0%; 95% CI, -5% to 65%). Vaccine effectiveness was strongly related to age at vaccination: 83% (95% CI, 39%-96%) for ages 15 through 20 years, 75% (95% CI, -17% to 93%) for ages 10 through 14 years, and 41% (95% CI, -106% to 79%) for ages 2 through 9 years. There was no evidence of protection in children younger than 2 years; all 8 MCD cases in this age group occurred in vaccinees. **CONCLUSIONS:** Serogroup C polysaccharide vaccine is effective for controlling outbreaks in teenaged individuals but should not be used in children younger than 2 years. The mass campaign did not induce significant serogroup switching.

Borrow R, Andrews N, Goldblatt D, Miller E. Serological basis for use of meningococcal serogroup C conjugate vaccines in the United Kingdom: reevaluation of correlates of protection. *Infect Immun.* 2001 Mar;69(3):1568-73.

The antibody data supporting the use of meningococcal serogroup C conjugate (MCC) vaccines in the United Kingdom were generated by serum bactericidal assay (SBA) using rabbit complement (rSBA). This may give higher titers than those obtained with human complement (hSBA), for which the "gold standard" correlate of protection for meningococcal C disease is a titer of ≥ 4 . Comparison of rSBA and hSBA titers in sera from unvaccinated adults with an rSBA titer of ≥ 8 showed that for 93% (27 of 29) the titer was ≥ 4 by hSBA, confirming natural protection. Furthermore, sera from MCC vaccinees showed that an rSBA titer of < 8 or ≥ 128 discriminated susceptibility and protection well (85% with rSBA titers of < 8 had hSBA titers of < 4 , and 99% with rSBA titers of ≥ 128 had hSBA titers of ≥ 4). However, discrimination was poor in the rSBA titer range 8 to 64, with only 60% having hSBA titers of ≥ 4 . In such cases we propose that protection can be assumed if there is a fourfold rise in titer between pre- and postvaccination sera or if there is a characteristic booster response to a polysaccharide challenge dose with, if available, evidence of antibody avidity maturation or an hSBA titer of result ≥ 4 . Applying these criteria to toddlers, 10 to 40% of whom had titers in the range 8 to 64 after a single dose of

MCC vaccine, showed that 94% had a fourfold rise in titer, including 98% of those in the titer range 8 to 64. In addition, of those with titers of <128 post-MCC vaccination, 90% had titers of > or =128 after a 10-microg polysaccharide booster dose, compared with only 7% of unprimed age-matched toddlers given a full 50-microg dose. Furthermore, the increase in geometric mean avidity index pre- and postbooster was independent of post-primary MCC titer. These results indicated that the majority of toddlers with an rSBA titer between 8 and 64, and some of those with an hSBA result of <4, have mounted a protective immune response with the induction of immunological memory.

Miller E, Salisbury D, Ramsay M.

Planning, registration, and implementation of an immunisation campaign against meningococcal serogroup C disease in the UK: a success story. Vaccine. 2001 Oct 15;20 Suppl 1:S58-67.

The introduction of meningococcal C conjugate (MCC) vaccine in the UK in November 1999 as a routine 3 dose infant immunisation course, with a single catch-up dose for all children aged between 12 months and 17 years, was the result of an intensive 5 year collaborative research programme funded by the Department of Health for England and involving public bodies, academia and vaccine manufacturers. The research programme established the safety and immunogenicity of MCC vaccines in infants, toddlers, pre-school and school-aged children. The nature and frequency of common adverse events in school-aged children was similar to that after a booster dose of diphtheria and tetanus vaccine given to the same age groups. The recommendation that a single dose was adequate for children aged 12 months and above was based on antibody levels measured by serum bactericidal assay and evidence of induction of immunological memory as shown by maturation of antibody avidity. Licensure by the Medicines Control Agency was based on serological criteria alone without direct evidence of efficacy and has set a precedent for other meningococcal conjugate polysaccharide vaccines. Vaccine coverage of around 85% was achieved in the targeted age groups and has resulted in a drop in the incidence of serogroup C disease in these groups of over 80% within 18 months of the start of the vaccination programme. Early post-licensure efficacy estimates for toddlers and teenagers (88 and 96%, respectively, in the first 16 months after vaccination) validate the serological criteria used for licensure. Surveillance of the prevalent serogroups and serosubtypes among invasive case isolates has shown no evidence of any capsular switching to serogroup B during the first 18 months of the MCC vaccination programme.

Some WHO documents on meningococcal disease and vaccines

WHO Technical Report Series, No 904, 2002. Annex 2. Requirements for meningococcal polysaccharide vaccine (amendment 1999)

Control of epidemic meningococcal disease. WHO practical guidelines. 2nd edition. WHO/EMC/BAC/98/3/EN

Emergence of W135 Meningococcal Disease. Report of an WHO Consultation, Geneva, 17-18 September 2001. WHO/CDS/CSR/GAR/2002/EN

Case definitions: Meningococcal Disease and Viral Meningitis. Epidemiological Bulletin, Vol 22 No 4, Dec 2001.

Epidemics of meningococcal disease, African Meningitis Belt, 2001. Weekly Epidemiol Record 14 Sept 2001. 37(76) 281-288.