

Round Table

Meningococcal meningitis in sub-Saharan Africa: the case for mass and routine vaccination with available polysaccharide vaccines

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Abstract Endemic and epidemic group A meningococcal meningitis remains a major cause of morbidity and mortality in sub-Saharan Africa, despite the availability of the safe and inexpensive group A meningococcal polysaccharide vaccine, which is protective at all ages when administered as directed. Despite optimal therapy, meningococcal meningitis has a 10% fatality rate and at least 15% central nervous system damage. WHO's policy of epidemic containment prevents, at best, about 50% of cases and ignores endemic meningitis, which is estimated at 50 000 cases per year. The effectiveness of group A, C, W135, and Y capsular polysaccharides is the basis for recommending universal vaccination with group A meningococcal polysaccharide twice in infancy, followed by the four-valent vaccine in children aged two and six years. This could eliminate epidemic and endemic disease, prepare for the use of conjugates when they become available, and probably could have prevented the recent epidemics of groups A and W135 meningitis in Burkina Faso.

Keywords Meningitis, Meningococcal/epidemiology/prevention and control; Meningococcal vaccines/pharmacology; Endemic diseases/prevention and control; Mass immunization; Immunization programs; Africa South of the Sahara (*source: MeSH, NLM*).

Mots clés Méningite méningococcique/épidémiologie/prévention et contrôle; Vaccins antiméningococciques/pharmacologie; Maladie endémique/prévention et contrôle; Immunisation de masse; Programmes de vaccination; Afrique subsaharienne (*source: MeSH, BIREME*).

Palabras clave Meningitis meningocócica/epidemiología/prevenición y control; Vacunas meningocócicas/farmacología; Enfermedades endémicas/prevenición y control; Inmunización masiva; Programas de inmunización; Africa del Sur del Sahara (*fuente: DeCS, BIREME*).

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Introduction

In African countries, WHO has reported meningococcal disease totalling 704 000 cases in 1988–97; this is likely to be a significant underestimate. About 100 000 people died during this period, and in 1996, an epidemic of more than 180 000 cases occurred. “The exact scale of this epidemic is unknown, since only a proportion of families take their ill relatives to hospitals during outbreaks, either because of ignorance or for

fear of being stigmatized ... substantial number of cases of infection remain undetected or people die outside of a health facility and sometimes for sociopolitical gains, there may be under reporting” (1).

Epidemiology

Epidemic meningococcal meningitis starts as outbreaks in small villages during the dry and windy season in late January (2). This

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climate probably contributes to inflammation of the respiratory tract and spread of the organism. Within a village, an outbreak lasts about one month. Countrywide, epidemic meningitis lasts from January to March and persists for about 2–4 years. The “meningitis belt” has increased in size, the interval between epidemics has decreased, an epidemic occurred for the first time in a city (Nairobi) in 1989 (3), and group A meningococcal meningitis has spread to Mecca and throughout the world (4).

An inverse relation exists between age-related incidence of meningococcal meningitis and development of bactericidal (mostly capsular polysaccharide) antibodies (5). Meningococcal disease is rare in children aged up to three months. The peak incidence is at about age one year, and the disease is infrequent in those aged ≥ 30 years. During epidemics, the incidence in older children and young adults increases.

Age-related development of antibodies is stimulated by group A meningococci and by cross-reacting organisms. Individuals with a bactericidal titre of 1 in 4 (about 1.5 μg immunoglobulin G group A meningococcal polysaccharide antibodies) are immune (5).

Morbidity and mortality

The death rate of about 10% for “treated” meningococcal meningitis occurs even when the public is aware of the disease and health care is prompt (6). In sub-Saharan Africa, death rates as high as 30% have been reported (7). At least 75 000 children are likely to have sustained central nervous system injury after “cure” of their meningococcal meningitis (8). Most African patients are injected once with “oily” chloramphenicol, which is not recommended in developed countries.

Pathogenesis and immunity

Serogroups A, B, and C meningococci capsular polysaccharides account for about 90% of cases of meningitis, the remainder being caused by W135 and Y serogroups. Most epidemics have been caused by group A meningococci (9). Capsular polysaccharides shield meningococci from complement, and immunity requires a protective level of anticapsular polysaccharides to initiate bacteriolysis.

The immunologic properties of group A, B, and C polysaccharides differ in childhood. Group B polysaccharide is non-immunogenic. Unique among bacterial capsular polysaccharides, two injections of group A polysaccharide, starting at age three months, elicit a booster response that results in protective levels of antibody (10). Antibody levels elicited by group A meningococcal polysaccharide in African and American children aged 18–24 months were indistinguishable (11, 12). As a result of these comprehensive studies, group A polysaccharide has been licensed by many countries and certified by WHO (9). Group C polysaccharide does not elicit protective levels in children aged <2 years, and reinjection in this age group results in diminished antibody levels to this antigen: accordingly, group C polysaccharide is not indicated in children aged <2 years. At two years of age, primary injection or reinjection of group A and group C meningococcal polysaccharides elicit protective levels to about the age of five years. Both group A and C polysaccharides need another injection at five years to maintain protective levels (10, 13). In children aged >6

years, one injection of group A or C polysaccharide elicits long-lived protective antibody levels (14–16).

Efficacy of group A meningococcal polysaccharide in children aged <2 years

Only two controlled trials of group A meningococcal polysaccharide in children aged <2 years have been reported (16, 17). In New Zealand, “After two 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 during the 1987 epidemic period was 52% (95% confidence interval –330% to +95%) falling to 16% (–538% to +90%) after one year” (17). Unhappily, numerous statements from the literature, not data, refute these results.

Group A meningococcal polysaccharide during epidemics in Africa and Asia

Nigeria

In 1979, Nigeria suffered epidemic group A meningococcal meningitis for the third year in succession (18). Vaccine supplies were limited, so immunization was restricted to all children aged >1 year in villages with at least two cases of meningitis. The serological data (see above) reliably predicted that two injections would confer immunity in this age group.

“*Summary* — Members of nine villages, with a population of about 10 000, in which there had been cases of meningococcal disease, were vaccinated with 50 μg of group A and group C meningococcal polysaccharide vaccine. There were subsequently 10 cases of meningococcal disease in these villages, but only two of these patients had been vaccinated. In contrast, there were 39 cases of meningococcal disease in seven control villages with a similar population.” (18).

“*Results* — Only two patients who developed meningococcal disease had been vaccinated, and in both of these patients, symptoms began on the day of vaccination” (18).

These two cases were not failures. The efficacy of group A meningococcal polysaccharide was 100%, and vaccination of 80% of the villagers induced herd immunity. Similar results were obtained during a vaccination programme during an epidemic with group A meningopolysaccharide in Sweden (19).

Chad

In 1988 an epidemic of group A meningococcal meningitis occurred in Chad (20). Initially, populations considered to be “at risk” (schoolchildren and army workers) were immunized. The epidemic continued, so vaccination of the entire population aged >1 year started: one week later, the epidemic halted. “These results show (i) the failure of selective vaccination to halt the epidemic, (ii) the efficacy of the mass vaccination campaign at the whole population [level], and (iii) the feasibility in tropical Africa of such a mass campaign, which must be carried out in a few days [of the onset of an epidemic]”.

Kenya

In 1988 an outbreak in Kenya included the city of Nairobi. “The estimated vaccine efficacy was 87% (95% confidence interval, 67–95%). No significant difference in vaccine efficacy was detected between those <5 and >5 years old.” (3)

Prevention of group A meningococcal meningitis by routine vaccination

Vaccination of the entire population with group A meningococcal polysaccharide was suggested by Mohammed & Zaruba in 1974 and 1981 (21).

The Gambia. Prevention of an epidemic in the Gambia was reported in 1986 (22).

Benin. Epidemics in adjoining countries prompted group A meningococcal polysaccharide vaccination of the entire population of the departments of Atacora and Borgou (23). The people in the affected areas purchased the vaccine themselves (US\$ 0.50 per dose). Between 1993 and 1996, coverage reached or exceeded 60% in Atacora and 50% in Borgou. During 1994–97, no group A meningococcal epidemics occurred in Benin, whereas neighbouring Burkina Faso, Niger, Nigeria, and Togo experienced severe epidemics. “The cost for the community has been negligible, and the rational organization of the preventative immunization avoids the disorder induced by the installation of a mass vaccination after the onset of epidemics.” (23)

Niger. “In Niamey, Niger, meningococcal vaccination began in 1978 and detailed surveillance of meningitis started in 1981. When coverage rates were higher than 50%, the prevalence of group A meningococcal meningitis [was] low, although there was a concurrent epidemic in rural Niger. A massive outbreak of meningitis in Niamey in 1994–95 followed a six-year period during which the mean rate of coverage remained <25%. In the meningitis belt, preventative immunization should avoid a great number of deaths and be less expensive than mass immunization campaigns performed after epidemics have begun.” (7)

China versus Mongolia. Group A meningococcal epidemics occurred in China during 1957, 1966, and 1976 (24, 25). Routine vaccination of infants and school-aged children started in 1980 and is close to 100%. Since then, no epidemics have occurred, and the number of cases of group A meningococcal meningitis has declined to a few per year. Despite an effective trial in 1977, adjacent Mongolia does not vaccinate with group A meningococcal polysaccharide and experienced an epidemic in 1995 (26). Vaccination started in 1996 under supervision by the Centers for Disease Control and Prevention showed about 90% efficacy in children aged >1 year.

Prevention of household contacts

Vaccination of household contacts with group A meningococcal polysaccharide is recommended practice (27).

Duration of group A meningococcal polysaccharide vaccine-induced immunity

Reingold et al., which is cited extensively, report the duration of immunity conferred by group A meningococcal vaccine as short (28). Prompted by an epidemic in 1981, about 103 000 children aged three months–16 years were vaccinated once with group A and C capsular polysaccharide vaccine. Only some of the vaccinees received vaccination cards. Another 25 000 doses were given to unvaccinated schoolchildren in 1983. The numbers are expressed as approximate in thousands, because incomplete records were kept. Surveillance was not described, about half of case records in the main hospital were discarded, and serology was not studied.

Efficacy three years after vaccination was 92% in children aged 4–7 years and 75% in those aged 8–16 years (92% vs 75%, not significant) (28). Efficacy in children aged 1–3 years was 89% after one year and 22% after three years.

But WHO recommends two injections several months apart for children aged three months–two years, with a booster about one year later and again in children aged 5–6 years (9, 29, 30). No comment about the high degree of efficacy in children aged 5–16 years was made in the recommendations (11, 12, 14). Conclusions based on data presented by Reingold et al. about immunity conferred by group A meningococcal polysaccharide are invalid: would anyone consider one injection of diphtheria–tetanus–pertussis vaccine to be adequate?

The recommendation of WHO for epidemic control and not routine immunization for meningococcal meningitis in sub-Saharan Africa is not based upon data, experience, or logic but upon what WHO and Centers for Disease Control and Prevention think can be done rather than what should be done.

WHO strategy for group A meningococcal meningitis in sub-Saharan Africa

A rate of 15 cases per 100 000 per week for two weeks provokes vaccination of children aged >2 years with one injection of group A and C capsular polysaccharides (31). This sentinel strategy failed to prevent the 1996 epidemic in Nigeria. In 1997, the Sudan endured about 32 000 cases and 2 200 deaths and Ghana 18 703 cases and about 1400 deaths (this was followed by an epidemic in 2001) (32). Accordingly, the threshold for sentinel strategies was lowered to 5–10 cases per 100 000 per week for two weeks (33–35). Epidemic control is faulted for the following reasons:

- At best only 50% of cases are prevented. WHO practices a double standard, because about 25 000 endemic cases of group A meningococcal meningitis per year would be considered “epidemic” in developed countries.
- At least 15% of “cured” meningitis cases suffer central nervous system injury. Group A meningococcal meningitis is a leading cause of mental retardation in Africa.
- Who will store group A meningococcal polysaccharide at –70° C for 10 years; maintain the equipment, staff, and cold chain necessary for emergency vaccination during an epidemic; and record to whom and when group A meningococcal polysaccharide is given?
- Epidemics start as outbreaks in rural villages. When reported, an epidemic has already started, and mobilization of personnel, vaccine, and the cold chain are needed. An epidemic has waned once vaccination is established. Delays of five weeks between detection and vaccination are reported (35).
- Resources would be more effective for routine vaccination within existing programmes than surveillance throughout the meningitis belt.

Inaccurate assertions about group A meningococcal polysaccharide are illustrated by WHO’s response to the 1997 epidemic in Ghana (32). In total, 18 703 cases occurred within three months: the overall incidence was 0.55%, with 7.2% mortality. Vaccine was delivered on 15 February, 15 March, and 22 March 1997. On the basis of assumptions, one week was required for vaccine distribution and one week to induce protection; only 33% of the vaccine was deployed by the peak (15 March) and the remaining 67% by 6 April — after the epidemic had subsided. The

response was tardy and incomplete despite five weeks' warning from an epidemic in adjacent Togo and the worst ever epidemic in West Africa during the previous year. Incomplete records of who received the vaccine, unproved assumptions and models, and disingenuous interpretation of data were used to propose that 72% of the "at-risk" population was vaccinated, 23% of cases and 18% of deaths were prevented, and routine immunization would have prevented only 61% of cases. Evaluation without these data is not credible (36). If mass vaccination had started six months earlier, there probably would have been no epidemic (7, 37–39).

Recommendations for mass and routine vaccination with group A meningococcal polysaccharide are not new

What could explain the inaccurate descriptions of the immunogenicity and efficacy of group A meningococcal polysaccharide?

- Overzealous touting of a candidate vaccine (38)?
- Overemphasis of cost–benefit analyses or the difficulty of implementing another routine vaccination (39)?

Routine vaccination with meningococcal vaccine would be more cost effective than WHO's strategy of epidemic control (7, 38–41).

W135 meningitis in travellers from the Haj occurred in Burkina Faso, Cameroon, and Niger, at the end of a group A meningococcal epidemic in 2000–01: most cases were aged <15 years (42–44). A similar situation was reported in 1980 (45). Routine A, C, W135, and Y vaccination would have prevented this tragedy: W135 and Y are infrequent causes of meningitis and their vaccines were licensed based on their immunogenicity in adults (45, 46) because both provide faultless immunity of armed forces. W135 and Y capsular polysaccharides elicit bactericidal antibodies in children aged >2 years (47).

The improved properties of meningococcal polysaccharide conjugates speak for themselves, but the safe, protective, inexpensive, and available group A meningococcal polysaccharide should be administered now within the Extended Programme on Immunization along with diphtheria–tetanus–pertussis vaccine to children aged one year and with A, C, Y, and W135 in children aged 2–5 years. Institution of routine vaccination with polysaccharide will enlarge the facilities for surveillance and facilitate introduction of conjugate vaccines (29, 30). The West African Health Organization will consider routine vaccination of schoolchildren with group A meningococcal polysaccharide.

Addendum

One objection to routine vaccination is that the slightly different schedule required for meningococcal polysaccharide vaccines might compromise existing programmes. Dr Ciro de Quadros of the Pan American Health Organization recalled the experience of Dr Albert Sabin in bringing polio vaccination to all children (47). Oral polio vaccine became available in 1965, and routine vaccination was implemented in developed countries in the late 1960s. Paralytic polio continued, however, in developing countries. The inability to vaccinate all children against polio was blamed on limited personnel and funds. Sabin campaigned to supplement health personnel with volunteers to focus nationwide publicity for a short period. This strategy was adopted in the 1990s and elimination of paralytic polio is close. The success of mass vaccination against polio strengthened rather than weakened programmes. ■

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Note: References 29 and 30 contain comprehensive bibliographies on this subject.

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Résumé

Méningite à méningocoque en Afrique subsaharienne : justification de la vaccination de masse et de la vaccination systématique avec les vaccins polyosidiques disponibles

A l'état endémique ou sous forme d'épidémies, les méningites à méningocoque du groupe A restent une cause majeure de morbidité et de mortalité en Afrique subsaharienne, malgré la disponibilité d'un vaccin antiméningococcique A polyosidique bon marché et sûr qui protège de la maladie à tous les âges s'il est administré en respectant le mode d'emploi. Même avec un traitement optimal, la méningite à méningocoque a un taux de létalité de 10 % et provoque dans 15 % des cas des lésions du système nerveux central. La politique de l'OMS pour endiguer les épidémies ne permet d'éviter au mieux que 50 % des cas et elle ignore la méningite endémique, responsable de 50 000 cas

par an selon les estimations. La recommandation d'une vaccination universelle par l'administration d'un polyoside méningococcique A deux fois avant l'âge d'un an se fonde sur l'efficacité des polyosides capsulaires A, C, W-135 et Y. Elle doit être suivie par l'administration du vaccin tétravalent à deux et six ans. Cette mesure permettrait d'éliminer les épidémies et la méningite endémique, de se préparer à utiliser les vaccins conjugués lorsqu'ils seront disponibles et elle aurait probablement évité les épidémies récentes de méningite A et W-135 au Burkina Faso.

Resumen

Meningitis meningocócica en el África subsahariana: justificación de la vacunación masiva y rutinaria con las vacunas de polisacáridos disponibles

La meningitis endémica y epidémica por meningococos del grupo A sigue siendo una importante causa de morbilidad y mortalidad en el África subsahariana, pese a la disponibilidad de la vacuna

de polisacáridos de meningococos del grupo A, que es barata y segura y proporciona protección en todos los grupos de edad cuando se administra de acuerdo con las instrucciones. Incluso con

un tratamiento óptimo, la meningitis meningocócica tiene una tasa de letalidad del 10% y produce lesiones del sistema nervioso central en al menos un 15% de los pacientes. En el mejor de los casos, la política de la OMS de contención de las epidemias evita aproximadamente un 50% de los casos e ignora la meningitis endémica, que produce unos 50 000 casos anuales. La recomendación de proceder a la vacunación universal con el polisacárido del meningococo del grupo A dos veces durante la

lactancia, seguida de la administración de la vacuna tetravalente a los niños de 2 y 6 años, se fundamenta en la eficacia de los polisacáridos capsulares de los grupos A, C, W135 e Y. Esto permitiría eliminar la enfermedad, tanto epidémica como endémica, y preparar el terreno para el uso de conjugados cuando estén disponibles, y probablemente hubiera evitado la reciente epidemia de meningitis por meningococos de los grupos A y W135 registrada en Burkina Faso.

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