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/prevención y control; Vacunas meningocócicas/farmacología; Enfermedades endémicas/prevención y control; Inmunización masiva; Programas de inmunización; Africa del Sur del Sahara (*fuente: DeCS, BIREME*).

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Voir page 748 le résumé en français. En la página 748 figura un resumen en español. يمكن الاطلاع على الملخص بالعربية في صفحة ٧٤٩

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, poulations 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 .

Conflicts of interest: none declared.

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.

ملخص

التهاب السحايا بالمكورات السحائية في البلدان الواقعة جنوب الصحراء الأفريقية. حالة التلقيح الجموعي النظامي باللقاحات المتوافرة العديدة السكاريدات.

الخلاصة: لا يزال التهاب السحايا بالمكورات السحائية يمثل السبب الرئيسي للمراضة والوافيات في البلدان الواقعة جنوب الصحراء الأفريقية، رغم توافر لقاح مأمون ورخيص من اللقاحات العديدة السكاريدات ضد المكورات السحائية من المجموعة A يقدم الوقاية لكافة الأعمار إذا ما أعطي وفق التعليمات. ورغم المعالجة المثالية فإن معدلات الوفيات الناجمة عن التهاب السحايا بالمكورات السحائية تبلغ ١٠٪ فيما لا تقل معدلات التخرب في الجملة العصبية المركزية عن ١٥٪.

وتؤدي السياسة التي تتبعها منظمة الصحة العالمية لاحتواء الوباء لاتقاء ٥٠٪ من الحالات في أفضل الأحوال مع تجاهل التهاب السحائي المتوطن والذي تقدر حالاته كل عام بخمسين ألف حالة سنوياً. وتعد فعالية عديدات السكاريدات من محافظ الجراثيم من المجموعات A و C و W135 و Y الأساس للتوصية بالتلقيح المعمم بعديدات السكاريدات للمجموعة A مرتين أثناء مرحلة الرضاعة، يتلو ذلك التلقيح بلقاح رباعي التكافؤ للأطفال الذين تتراوح أعمارهم بين سنتين وست سنوات. فذلك من شأنه أن يتخلص من المرض الوبائي والمتوطن، ويهيء لاستخدام اللقاحات المقترنة عند توافرها، وقد يقي من الأوبئة الحديثة الناجمة المجموعتين A و W135 في بوركينا فاسو.

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Round Table Discussion

Routine vaccination with polysaccharide meningococcal vaccines is an ineffective and possibly harmful strategy

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"*For every complex problem, there is an answer that is clear, simple, and wrong*"
(Menchen HL, 1880–1956)

Robbins et al. suggest that mass campaigns followed by routine vaccination in the meningitis belt would be more effective against epidemic and endemic meningococcal meningitis than the current outbreak response strategy. They propose two doses of group A meningococcal polysaccharide vaccine for routine infant immunization and two booster doses of tetravalent (A, C, W135, and Y) polysaccharide vaccine at two and five years of age. In our view, this strategy is ill conceived for numerous programmatic and epidemiological reasons and would not prevent meningitis epidemics (*1–4*).

The "case for mass followed by routine" vaccination presented by Robbins et al. is difficult to assess for several reasons: despite the article's title, the authors do not describe a target age group for mass vaccination, the frequency of campaign activities, and the estimated costs. The authors misrepresent WHO policy, as the recommended surveillance thresholds for action in the face of a meningitis epidemic have been revised for a more timely and effective response (*5, 6*). Implementation of the WHO recommended strategy with the more sensitive epidemic thresholds has been shown to avert a large proportion of potential cases (*7*). Robbins et al. also suggest that routine preventive vaccination would be effective, when in fact many studies have described the short-lived immunity provided by group A meningococcal polysaccharide vaccine, its poor immunogenicity in young children, and the fact that multiple doses of group A meningococcal polysaccharide vaccine in childhood actually may attenuate the serum bactericidal antibody response to *Neisseria meningitidis* group A (*8–11*).

Introducing group A meningococcal polysaccharide vaccine into routine infant immunization services will fail as a strategy to prevent meningitis epidemics, as most countries in the belt do not currently attain high vaccination coverage (Table 1) (*12*). Repeated follow-up mass campaigns would also be needed to "mop up" the large numbers of people susceptible to meningitis because they have not been vaccinated, because of waning immunity, and because of failure of group A meningococcal polysaccharide vaccine. As countries in the meningitis belt do not have policies in place for vaccinating children at two and five years of age (Table 1), the booster doses recommended by Robbins et al. would need revision of national policies and additional resources. The current immunization schedule would need to be expanded to include two doses of a vaccine that is poorly immunogenic in infants and two additional health contacts to provide the booster doses beyond the current five immunization contacts at birth, six weeks, 10 weeks, 14 weeks, and nine months.

Table 1. **Coverage with a third dose of diphtheria–tetanus–pertussis vaccine and booster dose policy for countries in the meningitis belt in 2001** (*12*)

Country	Diphtheria–tetanus–pertussis coverage (%)	Booster dose policy	
		Aged two years	Aged five years
Burkina Faso	41	No	No
Chad	36	No	No
Côte d'Ivoire	57	No	No
Ethiopia	56	No	No
Gambia	96	Yes	No
Ghana	80	No	No
Guinea	43	No	No
Guinea-Bissau	47	No	No
Mali	51	No	No
Niger	31	No	No
Nigeria	26	No	No
Senegal	52	No	No
Sudan	46	No	No

Robbins et al. do not mention the opportunity costs of the proposed strategy, particularly in light of the ongoing struggles in countries of the belt to finance more effective vaccines that protect against other lethal diseases. The authors state that group A meningococcal polysaccharide vaccine is inexpensive and widely available, however, no monovalent group A meningoccocal vaccine is licensed. At US$ 0.40 per dose, the cost of two doses of bivalent (A and C) meningococcal vaccine plus two additional booster doses of tetravalent polysaccharide vaccine (starting from US$ 2.50 per dose) is more than most countries in the belt spend on all other antigens combined. The trivalent (A, C, and W135) meningococcal vaccine currently used in Burkina Faso for epidemic control costs over US$ 1 per dose. Given that repeated follow-up mass campaigns also would be needed to prevent outbreaks, the cost of the proposed strategy would need massive mobilization of resources.

Finally, a more effective, long-lasting meningococcal A conjugate vaccine under development should be available by 2007, and this new vaccine will be well suited for integration into the current infant immunization schedule. By the time the strategy proposed by Robbins et al. could be put in place,

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therefore, it likely would be outdated because of the new, more effective conjugate vaccine.

In summary, the proposed strategy is ineffective and possibly harmful, based on known facts about group A meningococcal polysaccharide vaccine and the practical realities of health interventions in countries of the meningitis belt. Resources would be better spent strengthening immunization services and surveillance in these countries, so that the conjugate meningococcal vaccine can be introduced rapidly when available, offering the maximum and measurable public health impact expected. ■

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Conjugate meningococcal vaccines offer a much more promising alternative

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We agree with Robbins et al. that meningococcal disease has posed a recurrent public health problem in the African "meningitis belt" for at least 100 years. This region is characterized by a distinct pattern of meningococcal disease, with annual peaks of disease during the dry season at a rate several times higher than those in industrialized countries, and intermittent epidemics, with attack rates that can exceed 1% of the population (*1*). These epidemics cause substantial morbidity and mortality, but they also divert essential services and personnel and strain health infrastructures. Better control of both epidemic and endemic disease clearly is a public health priority.

A vaccine for meningococcal disease in Africa should be efficacious, induce immunological memory, have prolonged duration of protection, and provide herd immunity. In addition, vaccine use should be easy to operationalize and, optimally, the vaccine should be inexpensive. Currently, only three polysaccharide vaccine formulations are licensed and available to protect against serogroup A; bivalent group A plus group C; trivalent A, C, and W135; and quadrivalent A, C, Y, and W135. Serogroup A and C meningococcal polysaccharide vaccines have good immunogenicity and clinical efficacy in older children and adults (*2, 3*); however, they are poorly immunogenic in young children, do not reliably induce immunological memory, and provide protection of limited duration — especially in young children (*4*). The response of infants to additional doses suggests that repeated vaccination could be effective in providing short-term protection at all ages (*5*), but no studies have evaluated the long-term efficacy of a multidose regimen. Multiple studies have also failed to show substantial durable impact on nasopharyngeal carriage or induction of herd immunity. In addition, although reduced clinical efficacy has not been shown among people who have received multiple doses of vaccine, recent studies have raised the question of immunological tolerance to both serogroup A and C polysaccharide vaccines (*6, 7*). Robbins et al. suggest a four-dose regimen with doses at ages two and four; however, medical visits and interventions are not scheduled regularly at these ages in the affected regions of Africa, and this would make their approach difficult to operationalize. Finally, although the bivalent polysaccharide is inexpensive, the market price of the quadrivalent vaccine is US$ 2.50 per dose, and supplies of all three polysaccharide vaccines are quite limited.

More widespread use of polysaccharide vaccine may prevent some cases of meningococcal disease, but vaccination of children aged ⩽4 years will not target the approximately 70% of cases that occur in those aged >5 years (*8*). A preventive strategy with polysaccharide vaccine would require repeated mass vaccination, and even that strategy has failed to prevent epidemics in the past (*4, 9*). The limitations of meningococcal polysaccharide vaccines, as well as the limited supply of vaccines containing serogroup W135, means that the best strategy for their use remains a threshold-based approach that uses surveillance data to rapidly prompt mass vaccination campaigns (*10*). Optimization of this strategy will continue to need strengthening of laboratory-based surveillance and infrastructure for response.

In contrast with the polysaccharide vaccine, conjugate A and C meningococcal vaccines induce good immunogenicity in all age groups with a qualitatively different immune response and immunological memory (*11*). In the United Kingdom, where a serogroup C conjugate vaccine was introduced in late 1999, data shows good efficacy in all age groups, as well as reduction of nasopharyngeal carriage and induction of herd immunity (*12, 13*). If, as expected, these conjugate vaccines prove capable of providing a durable antibody response,

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particularly in infants and young children, integrating them into routine childhood immunization in the meningitis belt certainly would be warranted. These properties of conjugate meningococcal vaccines mean they should be more easily operationalized. Meningococcal Vaccine Project has negotiated production of a serogroup A meningococcal conjugate vaccine at less than US$ 0.50 per dose — a price equivalent to that of the bivalent (A plus C) polysaccharide vaccine (*14*). A number of large pharmaceutical companies also are developing serogroup A conjugate vaccines; consideration should also be given now to strategies for cost control. Although strategic issues regarding their use are unresolved, the characteristics of meningococcal conjugate vaccines have the potential to have a dramatic impact on both endemic and epidemic meningococcal disease throughout the world. ■

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Control of epidemic meningitis in sub-Saharan Africa: our solution is more practical and affordable

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Robbins et al. propose mass vaccinations with a group A polysaccharide vaccine (target population not stated) plus a four-dose vaccination schedule for children aged <7 years with divalent polysaccharide vaccines as a strategy for preventing group A meningococcal meningitis epidemics in sub-Saharan Africa. Two doses of group A polysaccharide vaccine would be given to children aged <1 year and booster doses with a quadrivalent (A, C, W135, and Y) polysaccharide vaccine at ages two and six years. This flood of polysaccharide vaccine, if given as indicated, would likely eliminate epidemic group A meningococcal meningitis in sub-Saharan Africa; however, the more important consideration is whether the strategy is feasible, fundable, and a sound investment in an area with limited resources.

I view the strategy as expensive and impractical. First, group A polysaccharide vaccine is currently not available on the market — a group A and group C polysaccharide vaccine can be bought for US$ 0.35 per dose, but it is not recommended for children aged <1 year. Second, the quadrivalent polysaccharide vaccine is available only in limited quantities and costs US$ 3.50 per dose. Third, sub-Saharan countries have the lowest immunization rates for children aged <1 year globally. For Robbins et al.'s strategy to work, under one year immunization coverage must be high, as must the coverage of booster doses at ages two and six years. In short, the scheme is unworkable. Strengthening routine EPI services would be a more sound short-term investment.

A more attractive strategy for the control of epidemic group A meningococcal meningitis is based on the development and use of conjugate meningococcal vaccines. The Meningitis Vaccine Project — a Gates Foundation-funded partnership between WHO and Program for Appropriate Technology in Health (PATH) — is developing a conjugate A meningococcal vaccine that will be available in 2007 and will be priced at about US$ 0.40 per dose (*1*). Meningitis Vaccine Project's strategy is based on the laboratory work of Robbins et al., who have shown clearly the superiority of conjugate over polysaccharide vaccines (*2*). This concept has been demonstrated amply by the fact that widespread use of conjugate *Haemophilus influenzae* type b vaccines has virtually eliminated *Hemophilus influenzae* meningitis as a public health problem (*3*). The recent experience in the United Kingdom with a conjugate meningococcal group C vaccine has also shown a profound effect in the incidence and carriage of disease after a single dose of vaccine (*4*). Along these lines, the strategic approach that will be implemented and evaluated by Meningitis Vaccine Project will begin with a comprehensive immunization of people aged 1–29 years with a single dose of conjugate A vaccine, coupled with a two-dose immunization schedule in children aged <1 year. The latter intervention will be integrated into the Expanded Programme of Immunization (EPI) schedule and is expected to result in a rapid and sustained decrease in transmission of group A *Neisseria meningitidis*. Recognizing the realities of low coverage in several meningitis belt countries, the timing of follow-up campaigns will depend on the level of coverage achieved in

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those aged <1 year. This strategy is affordable, is supported by African public health officials, and is consistent with the economic and logistic realities of delivering public health services in Africa *(5)*. Field trials of conjugate meningococcal vaccines will begin this year. The development, testing, and introduction of these vaccines constitute the best option for affordable and sustainable control of epidemic group A meningococcal meningitis in sub-Saharan Africa. ■

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Successful prevention of meningitis in Africa will need more than a vaccination strategy

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Since 1997, Robbins et al. have cogently argued that routine immunization with group A polysaccharide in sub-Saharan Africa would prevent epidemic and endemic meningitis (*1, 2*). Others have claimed that this recommendation rests on unproven assumptions and would be difficult to implement within existing immunization frameworks (*3, 4*). Understandably frustrated because of a lack of response by political agencies plus continued epidemics in Africa, Robbins et al. now repeat the same arguments in more detail. Unfortunately, their article is flawed, because it is highly polemic and contains numerous inappropriate or inaccurately represented citations. For example, routine immunization in northern Benin is inferred to have prevented meningitis epidemics through 1997 (*5*); however, acceptable levels of routine immunization in northern Benin were not maintainable for more than a few years (*5*). Contrary to Robbins et al.'s claim for long-lived immunity in vaccinees aged >5 years, routine immunization in the mid-1990s did not prevent a major epidemic in northern Benin in 2001 (*6*). Similarly, the primary citation for the efficacy of two doses of group A polysaccharide in infants does indeed claim that no cases were observed in such infants, but it also states "at the most only one to two cases would have been expected" (*7*). Such citations do not warrant initiating routine immunization with four doses of group A polysaccharide throughout sub-Saharan Africa.

The current practice of implementing mass vaccination once threshold levels of meningococcal disease have been exceeded enables short-term political decisions and possibly can be justified by cost–benefit calculations. It does not prevent epidemics (or endemic disease), however, nor has it been very effective at stopping major epidemics in Africa. Clearly, the ideal situation would be routine vaccination with an effective multi-component vaccine that provides long-lived immunity against meningitis. Such a vaccine does not yet exist, and the arguments below indicate that current efforts to develop a conjugated group A polysaccharide vaccine will not provide the ideal vaccine. History and molecular epidemiology teach that epidemic and endemic meningitis are only poorly predictable (*8–11*). Since the 1950s, successive waves of meningitis epidemics, each lasting for years, have been caused by subgroups I/II (1950s–70s), IV-1 (1980s), and III (late 1980s to present day). The first and last of these epidemic waves were imported from outside Africa because of the evolution of particularly fit and virulent meningococcal genoclouds (*11*). During both epidemic and endemic periods, a certain proportion of meningococcal disease also was caused by unrelated bacteria — sometimes of serogroups C, W135, and X (*12–14*). Only one-third of endemic bacterial meningitis in Africa is caused by meningococci, with the remainder caused by *Haemophilus influenzae* and *Streptococcus pneumoniae*. The prospects of finding an economically feasible and effective conjugated vaccine that can protect against all these agents are not good. Furthermore, medical interest in meningococcal meningitis and the motivation for routine vaccination tends to wane during endemic periods, which can be as long as 15–20 years in individual African countries.

Vaccines, and particularly conjugated polysaccharide vaccines, are the current paradigm for preventing infectious bacterial diseases in Africa. Yet improved housing, water, hygiene, and nutrition probably are the main factors that resulted in a general reduction in bacterial diseases in Europe and North America during the twentieth century, not vaccines (or antibiotics). Sub-Saharan Africa is lagging in these areas, and its load of general infectious disease remains extremely high. Levels of immunization that have eradicated epidemic infectious diseases, such as poliomyelitis, in Europe and North America still can permit the occurrence of epidemics in sub-Saharan Africa (*15*). According to this pessimistic prognosis, we will continue to be confronted with waves of epidemic meningitis in sub-Saharan Africa (and possibly China), regardless of the vaccine strategies that are implemented. Based on historical experience, however, I remain optimistic that the current wave of epidemic meningitis will terminate spontaneously in Africa in the near future. ■

Conflicts of interest: none declared.

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Meningococcal meningitis vaccination: more information needed

Sam Bugri[1]

We are uncertain about many factors surrounding meningococcal meningitis, which hinders the development of effective strategies for its control. For example:

- What is the relation between pharyngeal carriage rate in the population and epidemics?
- The meningitis belt has extended southwards in countries where the belt only covered the northern parts, such as Ghana. Globally, countries outside the belt (Angola, Burundi, Congo and Uganda) are reporting epidemics. Is the expansion of the meningitis belt related to the southward descent of the Sahel and to global climate change?
- Why do meningitis epidemics end with the beginning of the rainy season in the sub-Saharan countries?
- What level of antibodies after vaccination with polysaccharide vaccine is needed to provide protection?

Until we have more information on the above issues, WHO's strategy is the most feasible and affordable strategy for the control of epidemics of meningococcal meningitis. Some weaknesses do exist in WHO's strategy. It is dependent on recorded surveillance data, which we know is unreliable due to low patronage of health facilities in many countries. The criterion for initiating vaccination is the attack rate per district population crossing the set threshold. Poor surveillance means that the actual threshold often is crossed some weeks before the recorded surveillance data show this. Vaccination therefore often starts too late to have the desired impact. In the field, I have used the doubling of number of cases per week within a subdistrict's coverage or catchment area to initiate vaccination in that subdistrict. This was very effective, but the limited population, data, and number of cases would not satisfy the International Coordinating Group's criteria for the release of vaccines.

Robbins et al.'s argument is not convincing, especially in the light of the appearance this year of epidemics of serogroup A meningococcal meningitis after the pre-emptive mass vaccination of the total population in 2001 in Burkina Faso. If the epidemic in 2002 was mainly due to serogroup W135 because serogroup A had been suppressed by the vaccination campaign, why could it not suppress serogroup A again this year? At best, it seems that the polysaccharide vaccine is effective for one year only, and this makes it more suitable for the reactive vaccination recommended by WHO than for routine vaccination.

I will be convinced of the suitability of the polysaccharide vaccine for routine vaccination if:

- seroconversion and antibody surveys or surveillance showed the minimum level of antibodies needed to confer protection;
- two vaccinations with the polysaccharide vaccine a few weeks apart (with or without a later booster) were shown to stimulate high enough antibody levels that will stay high for more than five years; and
- the trivalent or quadrivalent vaccine will not cost more than the diphtheria, pertussis, and tetanus vaccine. ■

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