

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

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

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.

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 meningococcal 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. ■

Conflicts of interest: none declared.

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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. ■

Conflicts of interest: none declared.

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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. ■

Conflicts of interest: none declared

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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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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. ■

Conflicts of interest: none declared.

Meningococcal meningitis vaccination: more information needed

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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?

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