Eliminating Epidemic Group A Meningococcal Meningitis In Africa Through A New Vaccine

ABSTRACT A new affordable vaccine against Group A meningococcus, the most common cause of large and often fatal African epidemics of meningitis, was introduced in Burkina Faso, Mali, and Niger in 2010. Widespread use of the vaccine throughout much of Africa may prevent more than a million cases of meningitis over the next decade. The new vaccine is expected to be cost-saving when compared to current expenditures on these epidemics; for example, an analysis shows that introducing it in seven highly endemic countries could save $350 million or more over a decade. International donors have already committed funds to support the new vaccine’s introduction in Burkina Faso, Niger, and Mali, but an estimated US$400 million is needed to fund mass immunization campaigns in people ages 1–29 over six years in all twenty-five countries of the African meningitis belt. The vaccine’s low cost—less than fifty cents per dose—makes it possible for the affected countries themselves to purchase vaccines for future birth cohorts.

Bacterial meningitis is a serious infection of the thin lining surrounding the brain and spinal cord. Symptoms include a stiff neck, high fever, headache, and vomiting. Group A Neisseria meningitidis accounts for almost all epidemics (defined as incidence rates greater than 100 per 100,000 population) in the part of Africa where meningitis can be found. Other meningococcal strains (C/Y/W135) seen in Africa have historically accounted for only 10–20 percent of cases.

For more than a century, meningitis epidemics have regularly recurred across large sections of sub-Saharan Africa. As many as 450 million people are at risk. They live in twenty-five contiguous countries that constitute a “meningitis belt” stretching from Senegal in the west to Ethiopia in the east (Exhibit 1). About 240 million people live in the seven countries with the highest risk: Burkina Faso, Mali, Niger, Chad, northern Nigeria, Sudan, and Ethiopia. Surrounding countries have high-risk zones that abut the seven countries of greatest concern.

The epidemics most often attack children and young adults, with devastating results. Even with rapid diagnosis and treatment, 5–10 percent of patients die, typically within twenty-four to forty-eight hours of symptom onset. As many as a quarter of survivors are left with brain damage, profound hearing loss, learning problems, or other permanent disabilities. When the largest epidemic ever recorded spread through the region in 1996 and 1997, more than 250,000 people became ill, and 25,000 died. More than a million African cases of meningitis have been reported to the World Health Organization (WHO) since 1988, based on the WHO’s Integrated Disease Surveillance and Response data.

Bacteria belonging to the meningococcal family cause virtually all meningitis epidemics. Meningococci are carried at the back of the throat or nose and spread through the exchange of nasal and throat secretions during close or
intimate contact. Although most of the “carriers” remain healthy and do not develop the disease, in some cases the bacteria overcome the defense mechanisms of the immune system, invade the body, and cause serious illness. African epidemics occur annually during the dry season (January to May) and end with the first rains. In major epidemics as many as one in one hundred people fall ill in some communities.3

Effects Of Epidemics On Individuals And Communities
Without antibiotic therapy, the fatality rate for meningococcal meningitis can soar. Those fortunate enough to get to well-stocked health centers face their own challenges: Families must spend days away from home, often sleeping outdoors; work days are lost; fields go untended; and food and medicine must be purchased with scarce resources.

When medicine, nursing care, transportation to health services, lost wages, and other direct and indirect costs are tallied, a single case of meningitis may cost a Burkina Faso family about $90—the equivalent of three to four months’ income.5 Families without resources may be forced to sell their few possessions, which contributes to a downward cycle toward ever-greater poverty.

Epidemics also have profound negative effects on health systems. Responding to an epidemic supersedes all other health-related activities because frightened people—even the uninfected—demand care. Routine services cease at health centers. Campaigns to provide polio, measles, or yellow fever immunizations and other special programs are often delayed or postponed.6

Management Of Epidemics
In the past, countries have immunized communities after the onset of meningitis epidemics with

source Program for Appropriate Technology in Health.
the use of so-called polysaccharide vaccines. These vaccines are made from the outer coating of meningococci bacteria, which are largely composed of sugar molecules. Although these polysaccharide vaccines can prevent meningitis, they have several shortcomings: They protect the vaccinated for only two to three years, do not work well in infants and toddlers under two years of age, and do not block transmission of the organism from person to person. Moreover, the polysaccharide vaccines are typically in limited supply, and it is difficult to predict which vaccine will be needed, how much of it, and when.

Because the vaccine must usually be shipped long distances, getting vaccine to epidemic sites takes time. Often, limited quantities of polysaccharide vaccine arrive too late to do much good. Mass vaccination campaigns in one country reacting to an epidemic outbreak in 1996–97, for example, led to a modest 23 percent reduction in the number of cases and an 18 percent reduction in deaths.

The costs of mounting immunization campaigns in reaction to outbreaks are substantial. In 2007, for example, the cost to Burkina Faso for managing that year’s epidemic was US $9.43 million—5 percent of the country’s total health care budget. Also, because polysaccharide vaccines have not eliminated epidemics, countries must cope with the challenges of funding repeated reactive campaigns.

During the 2000 meningitis season, seven sub-Saharan countries and their donors spent US$60 million to purchase polysaccharide vaccine because of epidemics. Operational and other ancillary costs brought the total cost to about US$160 million. These large expenditures to combat meningitis epidemics have strained the health budgets of many countries in the meningitis belt.

Development Of A New Conjugate Vaccine

After the epidemic of 1996–97, African leaders turned to the WHO for help in solving the problem of epidemic meningitis. The WHO brought together global health leaders to discuss developing a new, more potent vaccine that could be used preventively and provide long-lasting protection against epidemic meningitis in Africa.

Previous research had shown that chemically linking (conjugating) a protein, such as diphtheria or tetanus toxoid, to a polysaccharide antigen results in a vaccine that is more powerful and capable of providing longer-lasting protection. This technique had previously been used to develop several meningococcal vaccines as well as vaccines against Haemophilus influenzae type B (a serious childhood disease that could cause meningitis or pneumonia) and pneumococcal infections. Conjugate vaccines have largely eliminated Group C meningococcal meningitis in the United Kingdom, Canada, Ireland, Spain, the Netherlands, and other developed countries since they entered the market in 1999.

In 2000 health experts from Africa and Eastern Mediterranean countries, multilateral organizations, vaccine manufacturers, and the scientific community concluded that developing a low-cost conjugate vaccine to fight Group A meningitis epidemics was not only possible but desirable. A year later the Bill & Melinda Gates Foundation provided a ten-year grant to establish the Meningitis Vaccine Project, a partnership between the WHO and the Program for Appropriate Technology in Health (PATH), a Seattle-based nongovernmental organization, to lead development, testing, licensure, and widespread introduction of a conjugate vaccine that could eliminate epidemic meningitis attributable to the Group A meningococcus.

Ensuring Affordability

In 2001, Meningitis Vaccine Project staff met with African public health officials, and the question of cost came quickly to the forefront. “Please don’t give us a vaccine that we can’t afford,” said Hassane Adamou, secretary general of Niger’s Ministry of Health. “That’s worse than no vaccine” (personal communication with Marc LaForce, 2002 Nov). To be sustainable in the countries where it would be used, the health officials said, the vaccine had to be affordable, which they defined in 2002 as costing less than US$0.50 per dose. As the Meningitis Vaccine Project team met with pharmaceutical companies to discuss developing a new vaccine for Africa, it became apparent that none of the firms in the developed world could produce the vaccine at the desired cost. The team began exploring alternatives.

Through a partnership with the Center for Biologics Evaluation and Research at the US Food and Drug Administration, the project team identified a new method for making conjugate vaccine. The technology was transferred at essentially no cost to the Serum Institute of India, a vaccine manufacturer with facilities in Pune. The institute agreed to produce the vaccine at an initial price of US$0.40 per dose, with future price increases tied to inflationary pressures. The Meningitis Vaccine Project also partnered with SynCo Bio Partners, a contract manufacturer in Amsterdam, to obtain a supply of purified capsular sugar (a polysaccharide) from Group A meningococci.
**Clinical Trials And Regulatory Approvals**

The project team conducted clinical trials in India and in meningitis-belt countries to test the vaccine’s safety and efficacy while strengthening countries’ capacity to host clinical trials. African scientists contributed to the design of study protocols and conducted trials in Mali, the Gambia, and Senegal. A Ghanaian study in infants is ongoing.27

Clinical trials confirmed that the new conjugate vaccine was safe and led to levels of antibody in the blood that were almost twenty times higher than levels obtained with the polysaccharide vaccine used in reactive immunization campaigns.18,19 By 2009 the Serum Institute of India had sufficient data from five clinical trials to submit the vaccine dossier to the Drugs Controller General of India for Indian licensure and to the WHO for prequalification for use in Africa. Through prequalification, the WHO licenses vaccines destined for UN agencies such as UNICEF for use in national immunization programs. In June 2010 the WHO prequalified the vaccine for use in people ages 1–29. Regulatory approval and WHO qualification of the vaccine for use in infants is anticipated in 2014.

Advantages of the new conjugate vaccine, called MenAfriVac, include the following: a more robust immune response against Group A meningococcus than seen with polysaccharide vaccines; the potential of long-lasting immunity after a single dose; the potential for safe and efficacious use among very young children when compared to responses to the previously used polysaccharide vaccine; potential for community (herd) immunity, as was noted after introduction of Group C meningitis conjugate vaccine in the United Kingdom and other European countries; and a cost of less than US$0.50 per dose, a price than would allow for sustained use of the vaccine to protect birth cohorts. Because of the project’s unique product development partnerships, discussed in a companion article in this issue of Health Affairs,20 MenAfriVac was developed at less than one-fifth the $500 million it typically costs to bring a new vaccine to market.

**Preparing For Introduction**

In September 2008 African ministers of health from meningitis-belt countries signed the Yaounde Declaration,21 which committed them to financially support fast-track introduction of the new meningococcal vaccine, strengthen meningitis surveillance, and improve information sharing across borders to enhance the region’s response to epidemic meningitis. To prepare for vaccine introduction, the WHO worked to build countries’ ability to integrate the new vaccine into their immunization programs. The WHO also led efforts to strengthen disease surveillance and to increase laboratory capacity to provide up-to-date information about meningitis outbreaks. An online e-learning tool for immunization managers in developing countries offered comprehensive, interactive information on meningococcal meningitis and the new vaccine.22

Three large pharmacovigilance studies were done in Mali, Burkina Faso, and Niger (about 1.2 million people) in September 2010.23 Data from these studies were reviewed by national committees and presented to the WHO’s Vaccine Safety Committee, which concluded that the new vaccine was safe and could be used in national campaigns.

Introduction of the new vaccine will use two strategies with different funding. The first strategy is an initial vaccination campaign of people ages 1–29 (about 70 percent of the total population in these countries) to rapidly establish herd immunity. Because of the size of this effort, support from donor agencies such as the GAVI Alliance (formerly known as the Global Alliance for Vaccines and Immunization) has always been part of the introduction plan.

Once these initial campaigns have been completed, countries will face the challenge of funding sustained use of the new vaccine to protect the next generations of newborns. At this stage of introduction, having an affordable vaccine price will be crucial.

GAVI is not intended to support ongoing funding for the new vaccine after the initial catch-up campaign. Country-specific funds using bilateral and country resources will need to support ongoing use of the vaccine, as reflected in the Yaounde Declaration. As noted above, regulatory approval to use the vaccine in infants may come as early as 2014. In countries with high rates of routine immunization, the new vaccine could be incorporated into the existing routine immunization calendar. In countries with low rates of routine immunization, follow-up single-dose campaigns targeting young children could be organized every five years.

**Launch Of Mass Immunization Campaigns In Three Countries**

The WHO and its partners developed a methodology to sequence the introduction of the vaccine. Countries were categorized according to case burden of disease, epidemic risk, and other factors. The first countries targeted for introduction were Burkina Faso, Niger, and Mali, because of their continuous high rates of incidence.
of meningitis A (a condition known as “hyperendemic”). To introduce the vaccine in these three countries, the GAVI Alliance provided US$29.5 million for vaccine purchase, planning, equipment, mass campaigns, training, and evaluation. UNICEF procured and supplied the new vaccine and facilitated its introduction.

In Burkina Faso, countrywide immunization campaigns with MenAfriVac began on December 6, 2010. Under the guidance of the Ministry of Health, 2,710 vaccination teams were deployed to immunize about eleven million people, starting with schoolchildren, in only ten days.

On December 10, Niger launched a ten-day vaccination campaign in ten of forty-two health districts. Almost three million people were vaccinated by 5,000 staff. And on December 16, Mali launched a similar two-week campaign in twenty-one health districts, during which 4.5 million Malians received the vaccine. By the end of 2010, vaccination had reached 19.5 million people in the three countries. 

The Meningitis Vaccine Project and its partners are working to assess the impact of mass immunization campaigns in the first introduction countries. Measuring impact is essential to show that the new vaccine works as expected; that its use saves money compared to costly emergency vaccination campaigns; and that funds given for the first introduction have been used to reach the target population and to reduce disease burden. Specific goals of the assessment include the following: accurately determining coverage rates; monitoring any adverse events following immunization; conducting case-based surveillance before and after introduction; determining the effect on carriage of Group A and other meningococcal strains; and conducting case-control studies to determine effectiveness.

### Rolling Out The Vaccine To Other Countries

Using health data, input from stakeholders, and assessments of country readiness, the WHO has developed a preliminary plan for rolling out the conjugate vaccine to other countries in the meningitis belt (Exhibit 2). Countries, however, will need to approve and lead subsequent vaccination campaigns. A review process will include WHO/GAVI subcommittee review of country proposals and a subsequent review by the International Coordinating Group on Vaccine Provision for Epidemic Meningitis Control, the group currently managing emergency meningococcal polysaccharide vaccine stockpiles.

For introduction to be successful, countries must be prepared. Preparatory steps include a detailed meningitis risk mapping exercise based on historical epidemiological data. Defining risk areas allows countries to estimate the target populations more precisely and prioritize vaccination sites if phased introduction is required. Potential sociocultural barriers and factors such as elections, other vaccination campaigns for measles, yellow fever or polio may affect demand for the vaccine and also need to be analyzed.

Additional preparation includes assessment of countries’ needs related to vaccine storage, a temperature-controlled supply chain of vaccines to ensure viability and shelf life, social mobilization and behavior-change communication, waste management, and logistics; identification of training needs; implementation of a system to monitor for adverse events following vaccination; and the development of a surveillance strategy that will include meningitis case surveillance with bacteriologic data.

Based on identified needs, countries will develop detailed budgets for fund-raising activities at national and international levels. Partner organizations will provide technical assistance. To receive support for introduction from the GAVI Alliance or other groups, countries must be responsible for half of the operational costs of mass vaccination campaigns with either in-kind contributions or country-based financing.

### Providing The Vaccine When And Where Needed

Ensuring that MenAfriVac is available in sufficient quantities when needed is a key issue affecting vaccine introduction. Although it is likely that the Serum Institute of India can provide up to forty million doses of vaccine during 2011 and as much as sixty million doses during 2012, orders must be placed early enough each year to ensure adequate time for vaccine production and delivery for campaigns that are held from October through December.

Availability of funding is the biggest obstacle to rapid vaccine rollout across the region. In large vaccination campaigns in Burkina Faso, Mali, and Niger, the cost per person vaccinated is estimated at about US$1.40. This figure includes vaccine and injection material, as well as operational and infrastructure costs. The estimated cost for the preliminary rollout plan for ten countries for the period 2011–2013 is US$238 million, including US$63.8 million in in-country financial commitments for operating costs. This would cover a target population of 170 million. PATH and the WHO hope to bring MenAfriVac to 250–300 million children and young adults in all twenty-five countries of the meningitis belt over the next five to ten years.

In a 2008 investment case prepared for the
GAVI Alliance, the total budget for immunization across the meningitis belt was estimated at $570 million over eight years, including in-country contributions of $182 million and a request for support from the GAVI Alliance for $370 million. The GAVI Alliance board has endorsed this strategy and approved $84.5 million for vaccination, although this included $55 million for meningitis epidemic response.

Because GAVI funding is constrained by the organization’s mission to support a broad range of immunization interventions, the successful rollout of MenAfriVac will depend on a robust fund-raising strategy. Nonetheless, it is important to emphasize that an important goal related to the affordability of the new vaccine is to ensure individual countries’ responsibility for protecting newborn cohorts after the large GAVI-supported campaigns have been completed.

The Case For Investing In Introduction Of The New Vaccine

The potential benefits of introducing MenAfriVac across the meningitis belt are enormous, both in reducing mortality and morbidity and in reducing costs associated with meningitis epidemics.

Using data from a population-based study in Niger, the Meningitis Vaccine Project team developed a Group A meningococcus disease burden model for a hypothetical hyperendemic country in the meningitis belt with a population of twelve million. The model is based on a number of reasonable assumptions and suggests that preventive use of MenAfriVac—compared to reactive use of polysaccharide vaccines—would prevent approximately 59,000 cases of meningitis, 7,100 deaths, and 14,200 permanent disabilities over ten years. These estimates presuppose that reactive use of polysaccharide vaccine reduces the number of cases by roughly 23 percent. Over the entire hyperendemic region (Burkina Faso, Mali, Niger, Chad, northern Nigeria, Sudan, and Ethiopia) with a population of about 240 million, use of the conjugate vaccine over a decade is estimated to prevent about 142,000 deaths and 284,000 permanent disabilities.

Until recently, meningitis outbreaks were con-
trolled with reactive vaccination campaigns; that is, campaigns were launched once epidemics had been recognized. The project team also developed cost estimates for introduction of MenAfriVac and compared these to the costs of reactive vaccinations (those done in response to an epidemic) over time. The team further considered potential savings in health care and laboratory costs associated with the introduction of the longer-lasting conjugate vaccine. The analysis shows major long-term cost savings associated with use of MenAfriVac to prevent epidemics in hyperendemic areas, even without including economic benefits from decreased deaths and disability. Most of the savings are associated with switching from a polysaccharide vaccine, which is less effective and must be given repeatedly, to a more potent conjugate vaccine that is effective for ten years or more. The analysis strongly suggests that conjugate vaccine introduction strategies are cost-effective and that the vaccine should be introduced into hyperendemic countries as soon as possible.

Exhibit 3 shows estimated costs for introducing MenAfriVac in seven hyperendemic countries over a ten-year period. Exhibit 4 shows potential savings from introduction of the conjugate vaccine—savings attributable mostly to eliminating the need for repeated purchase and administration of polysaccharide vaccine. The analysis suggests that widespread use of the conjugate vaccine could save $350 million or more over a decade.

An important caveat should be noted in articulating “savings” that accrue from no longer purchasing polysaccharide vaccine. Over the past twenty years, vaccine purchases in hyperendemic countries usually took place after the onset of a meningitis epidemic. Donations or purchases of vaccine occurred under urgent conditions. The introduction of the new meningococcal A conjugate vaccine will occur as a planned public health initiative, in the absence of an epidemic. Under such conditions, it may be

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**EXHIBIT 3**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost for introduction for country of 12 million population</th>
<th>Projected cost for hyperendemic region of 240 million population</th>
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</thead>
<tbody>
<tr>
<td>Men A conjugate vaccine catch-up (ages 1–29 years) plus 1 dose conjugate vaccine at 9–12 months*</td>
<td>$12.1 million</td>
<td>$242 million</td>
</tr>
<tr>
<td>Men A conjugate vaccine catch-up (ages 1–29 years) plus 2 doses conjugate at 14 weeks and 9–12 months *</td>
<td>$14.7 million</td>
<td>$294 million</td>
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<tr>
<td>Men A conjugate vaccine catch-up (ages 1–29 years) plus 2 follow-up campaigns (ages 1–4) in years 6 and 11</td>
<td>$15.1 million</td>
<td>$302 million</td>
</tr>
</tbody>
</table>

**SOURCE** Note 10 in text. **NOTE** Figures are US dollars. *A one-dose schedule (age 9–12 months) and a two-dose schedule (ages 14 weeks and 9–12 months) are being evaluated in ongoing clinical trials.

**EXHIBIT 4**

<table>
<thead>
<tr>
<th>Category</th>
<th>Projected savings for country of 12 million population</th>
<th>Projected savings for hyperendemic region of 240 million population</th>
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<tbody>
<tr>
<td>Health care</td>
<td>$2.8 million</td>
<td>$56 million</td>
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<tr>
<td>Laboratory</td>
<td>$0.24 million</td>
<td>$4.8 million</td>
</tr>
<tr>
<td>Polysaccharide vaccine purchases</td>
<td>$15.9 million</td>
<td>$318 million</td>
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<tr>
<td>Polysaccharide vaccine administration</td>
<td>$13.9 million</td>
<td>$278 million</td>
</tr>
<tr>
<td>Total potential savings</td>
<td>$32.84 million</td>
<td>$656.8 million</td>
</tr>
</tbody>
</table>

**SOURCE** Note 10 in text. **NOTE** Figures are US dollars.
more difficult to identify donor support for a conjugate vaccine to be given preventively.

Cost and savings calculations for introducing MenAfriVac in lower-risk meningitis-belt countries (such as Ghana and Côte d’Ivoire) are more uncertain than those in high-risk countries (such as Burkina Faso and Nigeria). The inadequacy of disease incidence and bacteriologic data makes it difficult to create accurate models for assessing costs and savings associated with introducing the conjugate vaccine.

Conclusion
An affordable, effective, long-lasting conjugate vaccine against Group A meningococcus offers extraordinary hope for wiping out epidemics of group A meningococcal meningitis in sub-Saharan Africa. A one-time investment to vaccinate populations throughout the meningitis belt could save more than 140,000 lives over the next decade and spare another 280,000 people from serious permanent disabilities, such as brain damage and profound hearing loss.

The GAVI Alliance and other groups have already committed funds to support the new vaccine’s introduction in Burkina Faso, Niger, and Mali. Yet the full promise of the vaccine to eliminate epidemic meningitis from sub-Saharan Africa can be realized only with an estimated US$475 million in additional funding. This provides an excellent opportunity for policy makers and donors to contribute to a momentous success in collaborative work to improve global health. The low cost of the vaccine will allow countries to sustain its use to protect newborn cohorts.

NOTES
is to eliminate epidemic meningitis from sub-Saharan Africa through the widespread use of conjugate meningococcal vaccines. (A conjugate vaccine is formulated by chemically linking sugar chains derived from the pathogen to a protein backbone.)

“The most important lesson we learned is the amazing power of partnerships when all members are committed to the same goal,” says LaForce.

Before joining the Meningitis Vaccine Project, LaForce held academic and administrative positions at the University of Colorado and the University of Rochester medical schools. From 1994 to 2001 he led the steering committee on epidemiology and field research for the WHO’s vaccine cluster. He earned his medical degree from Seton Hall College of Medicine and Dentistry and received internal medicine and infectious diseases training on the Harvard service at Boston City Hospital.

Jean-Marie Okwo-Bele is director of the Department of Immunization, Vaccines, and Biologicals at the WHO in Geneva since 2004. He oversees vaccine research, vaccine quality, and the safety of immunization policy. His team consists of 110 professionals and collaborates with the WHO network of vaccine teams in six regions and sixty-seven countries. Before that, he was chief of global immunization activities at UNICEF, among other positions.

During his thirty-year career in public health, he has worked on the expansion of immunization programs in many countries, including the polio eradication initiative in Africa. He is the coauthor of more than twenty articles and book chapters on vaccines and immunizations.

Okwo-Bele trained as a physician, receiving his medical degree from the National University of Zaire (currently Democratic Republic of the Congo) and a master of public health degree from the Johns Hopkins University.