

Evaluation of Serogroup A Meningococcal Vaccines in Africa: A Demonstration Project

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ABSTRACT

Endemic and epidemic meningococcal disease constitutes a major public-health problem in African countries of the 'meningitis belt' where incidence rates of the disease are many-fold higher (up to 25 cases per 100,000 population) than those in industrialized countries, and epidemics of meningococcal disease occur with rates as high as 1,000 cases per 100,000 people. Using the precedent established during the licensing of conjugate vaccines against *Haemophilus influenzae* type b and serogroup C meningococci and components of currently-licensed meningococcal polysaccharide vaccines, new meningococcal conjugate vaccines will likely be licensed using immunological endpoints as surrogates for clinical protection. Post-licensure evaluation of vaccine effectiveness will, therefore, be of increased importance. One vaccine being developed is the serogroup A meningococcal (Men A) conjugate vaccine produced by the Meningitis Vaccine Project (MVP), a partnership between the World Health Organization and the Program for Applied Technology in Health. This vaccine will likely be the first meningococcal conjugate vaccine introduced on a large scale in Africa. This paper summarizes the general steps required for vaccine development, reviews the use of immunogenicity criteria as a licensing strategy for new meningococcal vaccines, and discusses plans for evaluating the impact of a meningococcal A conjugate vaccine in Africa. Impact of this vaccine will be measured during a vaccine-demonstration project that will primarily measure the effectiveness of vaccine. Other studies will include evaluations of safety, vaccine coverage, impact on carriage and herd immunity, and prevention-effectiveness studies.

Key words: *Neisseria meningitidis*; Meningococcal vaccines; Conjugate vaccines; Vaccine development; Immunization; Evaluation studies; Impact studies; Africa

INTRODUCTION

One of the most significant accomplishments in medicine and public health is the development and use of vaccines for the prevention and control of infectious diseases of major public-health concern. This preventive

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approach is fundamental to improving health in developing countries, where curative services are scarce and disproportionately costly (1). Since the 1980s, considerable progress has been made in introducing and improving immunizations, especially among young children. As a result, almost three million lives are saved each year, and 750,000 children are saved from disability (2).

The main antigens used in immunization programmes in developing countries include those against measles, polio, pertussis, diphtheria, tetanus, and tuberculosis. Introducing newer vaccines has proven more difficult. One group of vaccines currently being developed and

introduced in these countries are conjugate vaccines against the three main causes of bacterial meningitis and pneumonia: *Streptococcus pneumoniae*, *Haemophilus influenzae* type b (Hib), and *Neisseria meningitidis* (3). These three bacteria, responsible for more than one million deaths per year, are a major cause of morbidity among children and young adults (4). Of these three bacteria, only *N. meningitidis* causes major epidemic disease, particularly in the 'African meningitis belt', an area that extends from Ethiopia in the East to Senegal in the West (5,6). Most of these epidemics are caused by serogroup A meningococci. Mortality from meningococcal meningitis is 8-12%, and 12-15% of survivors have long-term sequelae, such as hearing loss, neurological disability, or limb amputation (7,8).

In the African meningitis belt, rates of meningococcal disease are many-fold higher (up to 25 cases per 100,000 people) than those in industrialized countries, and epidemics of meningococcal disease in meningitis-belt countries occur with rates as high as 1,000 cases per 100,000 people. Disease occurs in annual cycles with large-scale epidemics every 8-12 years (5,6). In addition, during the past few decades, major epidemics have been reported in countries which are not usually considered part of the African meningitis belt, e.g. Kenya, Tanzania, and Rwanda (9). In 1996, the largest outbreak ever reported occurred in the meningitis belt; the total number of cases reported to the World Health Organization (WHO) (probably a substantial underestimate) was 152,813, with 15,783 deaths (10).

Meningococci are classified into serogroups according to immunologic reactivity of their capsular polysaccharides that are the basis for currently-licensed meningococcal vaccines. Worldwide, serogroups A, B, and C account for most cases of meningococcal disease with serogroups B and C responsible for the majority of disease in Europe and the Americas and serogroups A and C predominating throughout Asia and Africa. In the African meningitis belt, meningococcal disease is usually caused by serogroup A (5). In addition, epidemics caused by serogroup C, and more recently by serogroup W-135, have been reported (11,12).

Because of its epidemic potential and high endemic burden, meningococcal disease is a priority disease for prevention and control in Africa. In this paper, we review the general steps required to develop meningococcal vaccines and discuss plans for evaluation of a new meningococcal A conjugate vaccine in Africa.

VACCINE DEVELOPMENT

The success of a vaccine in preventing disease depends on potency, effectiveness, safety, and appropriate distribution and use. The vaccine-development process takes several years and includes multiple disciplines, such as pre-clinical and clinical testing, and regulatory issues (13-15). Pre-clinical testing focuses on detailed physico-chemical characterization of the vaccine and safety and immunogenicity in animals to support its use in humans. Once the safety and biological activity of the investigational vaccine has been evaluated in animals, phased clinical studies are conducted in humans.

Clinical trials in humans include phase I, phase II, and phase III studies (Table). The overall goal of these clinical studies is to establish: (a) the clinical tolerance and safety of the investigational vaccine, (b) the type, level, and persistence of immune response after its administration to a representative target population using a defined administration schedule, and (c) the clinical safety and efficacy of the investigational vaccine, where efficacy is defined as the outcome of clinical protection and/or immunological surrogate endpoints in phase III clinical trials (15). Phase III clinical studies involve the recruitment of a large number of study participants who will receive the investigational vaccine and another group of study participants who will receive an inert substance or unrelated vaccine (placebo); efficacy of vaccine is calculated directly from the number of cases occurring in each study group. Phase III randomized, controlled clinical trials are conducted under ideal study conditions to estimate the best possible efficacy and constitute the best approach for evaluating health interventions. However, because large samples and relatively prolonged and complete follow-up may be necessary for adequate statistical power, these studies often are very expensive and require lengthy follow-up.

While the first vaccine developed for a given disease is frequently evaluated in a phase III randomized, placebo-controlled trial, newer vaccine formulations in the United States and Europe have been licensed based on active-control immunogenicity trials, where the licensed vaccine is administered to the control group, and the experimental group receives the new formulation. Measurements of immunogenicity of capsular polysaccharide-based vaccines that are surrogates for protection are calculated through enzyme antibody concentrations, e.g. enzyme-linked immunoabsorbent assay (ELISA), antibody avidity, and functional antibody assays,

e.g. serum bactericidal activity and opsonophagocytic tests. In an active-control immunogenicity trial, 'non-inferiority' of the new vaccine may be evaluated by confirming that the effects in the investigational vaccine group are no worse than that in the control vaccine group by more than prescribed amounts (15-19). Polysaccharide and conjugate meningococcal vaccines and conjugate Hib vaccines have been licensed based on such studies (20-23).

POST-LICENSURE PHASE IV EFFECTIVENESS STUDIES

Following licensure, evaluation of safety and effectiveness of vaccine is referred to as post-marketing surveillance or post-licensure phase IV studies. The purpose of phase IV studies is to evaluate the performance and impact of a vac-

cine in the large target population under conditions of routine use. The main objective is to evaluate the effectiveness of vaccine, defined as the impact of the vaccine in a population, where the effects of vaccination will also depend on coverage, distribution of the vaccine and its efficacy in preventing disease and colonization (24).

The effectiveness of vaccine is measured through case-control and cohort studies, which constitute useful alternatives to placebo-controlled vaccine-efficacy trials. These studies measure the relative risk or odds ratio of disease among the vaccinated compared to the unvaccinated. Their design is based on four critical aspects: (a) case definitions, (b) case findings, (c) ascertainment of vaccination status, and (d) assuring comparability of vaccinated and unvaccinated groups (25).

Table. Main characteristics of phase I, II, and III studies in human clinical research (16)

Study	Purpose	Population under study	Study duration
Pre-licensure studies			
Phase I	To evaluate clinical tolerability and reactogenicity of vaccine	Small number of highly-selected normal healthy adult volunteers	Short duration
Phase II	To provide preliminary information on biological activity of elicited antibodies to predict vaccine efficacy using standardized serological assays	Larger numbers of individuals who may more closely resemble the ultimate target population	Medium duration
	To further evaluate safety		
	To evaluate immunological activity, and dose-ranging and 'optimal' schedules of vaccination		
Phase III	To provide clinical evidence of consistency of vaccine manufacturing	Large sample of individuals from the intended target population	Long duration for randomized placebo-controlled trials
	To demonstrate safety, efficacy, and clinical protection of vaccine in a large population		
	To evaluate immunogenicity using standardized serological assays		
Post-licensure studies	To assess duration of protection		Medium duration for active-control immunogenicity trials
	Phase IV	To evaluate impact of vaccine at population level, where effects of vaccination also depend on coverage, distribution of vaccine, and efficacy preventing disease and colonization	Overall population under surveillance Restricted sample of the population required for vaccine-effectiveness case-control study

Because these studies are non-experimental, they are particularly subject to bias. To keep potential biases to a minimum, case definitions used in post-licensure studies should be sensitive and specific for gaining the most precise estimate. When sensitivity is low, it will be important that case definitions have equal sensitivity in vaccinees and non-vaccinees and that case definition is specific through laboratory confirmation of cases. Specificity of case definition is usually more critical than sensitivity for accurately determining the effectiveness of vaccine. Appropriate case-finding also diminishes the potential of bias on cohort and case-control studies. Ideally, population-based case-finding or surveillance should be used. For severe diseases, such as meningitis, provider-based surveillance systems may be adequate, provided all patients, vaccinated or unvaccinated, seek medical care. Ascertainment and confirmation of vaccination status is another important aspect to consider for diminishing bias. Vaccination status should be verified using vaccination cards and vaccination registries. If vaccination records are lost or inaccurate, study participants can be misclassified in regard to their vaccination status, which can result in incorrect estimates of vaccine effectiveness. Finally, assuring comparability of vaccinees and non-vaccinees will be important to avoid potential confounding; such confounding can produce underestimates or overestimates of vaccine effectiveness and can even lead to negative estimates when the true effectiveness is positive. For case-control studies, matching of controls to cases on potential confounders, such as age, place of residence, or socioeconomic status, can adjust for differences in recognized potential confounders between cases and controls. Potential confounding can be avoided in cohort studies by collecting information ahead of time on vaccinees and non-vaccinees on variables known or suspected to be related to the risk of diseases. Subsequent analyses can be carried out separately for sub-groups that are comparable in terms of the potentially-confounding variable. The use of statistical techniques, such as stratification or logistic regression, can also be used for adjusting for confounding (25-28).

Case-control studies are often used for measuring the effectiveness of vaccine in the field because their design allows maximal resources to be applied to small numbers of cases and controls to accurately assess vaccine and history of disease, improving quality of data, and limiting misclassification errors. In addition, case-control studies allow identification of risk factors of

disease and later adjustment of potential confounding factors (25). Post-licensure vaccine studies also include assessments of safety, coverage, and impact of vaccine on carriage and herd immunity. Herd immunity is also assessed because conjugate vaccines are expected to have an impact on carriage, which would produce a reduction in exposure among unvaccinated persons and, therefore, an impact of the vaccine in reducing disease among non-vaccinated persons (herd immunity effect).

CURRENT AND FUTURE MENINGOCOCCAL VACCINES

With the exception of serogroup B, meningococcal polysaccharide vaccines have been developed against the other most common serogroups (A, C, Y, and W-135) causing disease. The first of these vaccines, against serogroups A and C, was produced in 1969 by Gotcshlich *et al.* (29). Since then, two bivalent A/C meningococcal polysaccharide vaccines have been licensed based on clinical efficacy data (30-32). Studies of serogroups Y and W-135 polysaccharides found them to be safe and immunogenic, and a tetravalent A/C/Y/W-135 meningococcal polysaccharide vaccine was licensed in the USA, despite lack of efficacy data, based on the principle that the new combination vaccine only added new serogroups to an already-licensed multivalent product (23,33). More recently, a trivalent A/C/W-135 meningococcal polysaccharide vaccine was licensed by Belgian regulatory authorities for use in Africa (34).

Meningococcal polysaccharide vaccines have inherent limitations (35). The C polysaccharide is poorly immunogenic in young children with little or no efficacy in children aged less than 24 months (36-38). The serogroup A polysaccharide induces some antibody response in infants and young children but efficacy of vaccine declines rapidly (39). In addition, meningococcal polysaccharide vaccines do not elicitate long-lasting immunity (39,40) and do not have a major impact on carriage (41,42). Lastly, repeated doses of meningococcal polysaccharide vaccines have been associated with hypo-responsiveness (43).

To overcome the limitations of polysaccharide vaccines, conjugate vaccines against meningococcal disease are under development. Conjugation of polysaccharides to proteins changes the nature of anti-polysaccharide immune response from T-independent to T-dependent, leading to a substantial primary response among infants and a strong booster response at re-exposure (20,35).

Since 1992, a series of safety and immunogenicity studies have evaluated bivalent A/C and quadrivalent A/C/Y/W-135 meningococcal conjugate vaccines (44-50). These studies have been remarkably consistent showing safety and improved immune response in infants. Induction of immunological memory is well-established for serogroup C and is being studied for the serogroup A polysaccharide.

In 1999, regulatory authorities in the UK licensed three serogroup C meningococcal conjugate vaccines, based on safety and immunogenicity data, without a phase III efficacy study (51). The basis of this decision was the existing licensure of plain serogroup C polysaccharide vaccines for children aged two years and above for whom there was direct evidence of efficacy and accepted serological correlates of protection. Correlates of protection were validated for infants (21,51). The serogroup C meningococcal conjugate vaccine was introduced in November 1999 for all children aged less than 18 years, and a post-licensure evaluation programme estimated that the serogroup C meningococcal conjugate vaccines used in the UK have had a dramatic impact on serogroup C disease (21). The effectiveness of vaccine was 96% (91-98%) (22,52,53). In addition, the vaccine reduced serogroup C nasopharyngeal carriage by 66% (54) and decreased disease by 52% in unvaccinated children and adolescents, demonstrating herd immunity (52).

Licensure for other new meningococcal conjugate vaccines will also likely be based on safety and immunogenicity data without phase III clinical efficacy studies. Protective efficacy of meningococcal conjugate vaccine will be inferred from immunological endpoints based on the following observations: (a) serum bactericidal activity constitutes a good indicator of clinical protection against serogroup A and serogroup C meningococcal disease (51,55); (b) serogroup A/C and A/C/Y/W-135 meningococcal polysaccharide vaccines were licensed for persons aged two years and above with serological correlates of protection (31-33,36); (c) safety and immunogenicity studies showed that serogroup A-containing conjugate vaccines are safe, improve immune response in infants, prime immunologic memory, and lead to a booster response to subsequent doses (48,44-47); (d) Hib conjugate vaccines are licensed for infants and children for whom there is post-licensure evidence of vaccine efficacy and effectiveness (48,56); and (e) serogroup C meningococcal

conjugate vaccine is licensed for infants and young adults for whom there are accepted serological correlates of protection and clinical efficacy of the vaccine has been demonstrated after licensure (22,53). In addition, randomized placebo-controlled phase III trials may be ethically and logistically difficult to conduct in African countries, especially in epidemic situations, where meningococcal polysaccharide vaccines have proven to have an impact in reducing incidence of disease, and where the priority will be on responding to the epidemic and saving lives.

POST-LICENSURE DEMONSTRATION PROJECT FOR MENINGOCOCCAL A CONJUGATE VACCINES IN AFRICA

Because pre-licensure studies of new meningococcal conjugate vaccines will not include evaluation of clinical vaccine protection, post-licensure evaluation of the vaccine is essential. A demonstration project will evaluate vaccine effectiveness in a real-world situation, providing information that can be used for stimulating the introduction and routine use of vaccines in African countries.

A serogroup A meningococcal (Men A) conjugate vaccine is currently being developed by the Meningitis Vaccine Project (MVP) with financial support from the Bill and Melinda Gates Foundation. Clinical lots of a Men A conjugate vaccine are anticipated in 2004, and phase I and II clinical studies will begin in 2005 and last through 2008 with licensure of the vaccine in 2009. The goal of MVP is to make available 25 million vaccine doses annually with a transfer vaccine price of about US\$ 0.40 per dose (57). The Men A vaccine will be primarily introduced through country-wide mass vaccination campaigns among persons aged 1-29 year(s); in addition, a Men A conjugate vaccine will be introduced as part of Expanded Programme on Immunization for children aged less than one year.

By 2009, the Men A conjugate vaccine will be introduced in selected African countries at high risk for epidemics of meningococcal disease. Retrospective epidemiological and laboratory data will be used for determining likelihood of epidemics of serogroup A meningococcal disease in the country or countries being considered for the introduction of the vaccine.

Among these 'early introducers', one country will be chosen to conduct a post-licensure demonstration project during the first year of vaccine introduction.

Selection criteria will include the existence of strong public-health infrastructure with epidemiological and laboratory surveillance systems able to implement and monitor Men A mass vaccination campaigns and to rapidly detect and bacteriologically confirm cases of meningococcal disease. The demonstration country should have the capacity to organize and carry out a major mass vaccination campaigns with the Men A conjugate vaccine. Necessary infrastructure will include use of vaccination cards and registries, trained vaccination teams, and plans for storage, transport, and administration of the vaccine. Because of the need to develop substantial infrastructure and the necessity of obtaining pre-vaccination baseline surveillance data, consideration should be given to the development of several demonstration sites so that the optimal site can then be chosen for the demonstration project.

Strong laboratory-based surveillance will be critical for the detection and confirmation of meningococcal disease cases and for the evaluation of vaccine effectiveness against serogroup A meningococcal disease. Laboratory-based surveillance will also be important to monitor meningococcal serogroups causing disease, detect other causes of bacterial meningitis (*S. pneumoniae* and *H. influenzae*) not preventable by a Men A conjugate vaccine, and monitor possible emergence of other meningococcal serogroups as a cause of epidemic disease. Laboratory surveillance will also allow implementation of accessory studies to evaluate carriage and seroprevalence. In addition, because of concern that hyper-invasive serogroup A and C meningococci may be replaced by vaccine escape variants or other virulent strains (54,58), laboratory-based surveillance will be needed to monitor changes in molecular epidemiology.

Ideally, the entire country selected for the demonstration project should have sufficient laboratory capacity to confirm all meningitis cases, but because this may not be realistic, selected districts within the country may be identified for the demonstration project. The following criteria may be used for selecting these districts: (a) capacity to accurately evaluate the quality of vaccination campaigns through analysis of vaccination cards or surveys, (b) sufficient health infrastructure to allow detection of suspected meningitis cases and collection of cerebrospinal fluid (CSF) samples in all suspected cases, (c) local laboratory infrastructure to allow Gram-staining and rapid serological testing on CSF samples using latex seroagglutination tests, (d) infra-

structure to facilitate rapid transport of CSF samples inoculated on transport media to a reference laboratory (national or provincial bacteriology laboratory), and (e) capability of reference laboratory (at regional or national level) to perform culture and serogrouping of meningococcal isolates. In addition, these districts should have the necessary infrastructure to support special studies, such as carriage and seroprevalence studies. An area with a population of at least two million will be required to provide adequate power to assess the effectiveness of the vaccine.

Effectiveness and impact of vaccine

Using a case-control study, the effectiveness of the vaccine will be measured by comparing the odds of being vaccinated among cases and matched controls in selected districts in the demonstration country using the formula $VE (\%) = (1 - OR) \times 100$, where VE is vaccine efficacy and OR is odds ratio (25). Cases will be defined as 'suspected', 'probable', and 'definite' and will be identified in districts where mass vaccination campaigns with a Men A conjugate vaccine will be taking place. Assessment and confirmation of vaccination status will necessitate use of vaccination cards during vaccination campaigns. Vaccination cards will be distributed during mass vaccination campaigns, and records on distribution of cards will be maintained. Cards will be completed and given to vaccinated persons at the vaccination site. The vaccination cards will include information on name and date of birth of person being vaccinated, district, type of vaccine received, and vaccine lot number. Vaccination status will be defined as 'verified' and 'reported'. Controls will be matched by age and residency with cases.

All clinically-suspected cases of meningitis will be evaluated and be laboratory-confirmed at the district and national laboratories. Eligible persons with confirmed meningococcal disease and matched controls will be enrolled and interviewed. Demographic, clinical and epidemiological data will be collected. To account for possible confounding, information on risk factors for meningococcal meningitis will also be collected. The case-control study will be implemented following similar to the methodology of a recently-conducted vaccine-effectiveness study in Burkina Faso (59).

In addition to the case-control study, the impact of the vaccine will be measured through cohort analysis of all clinically-suspected meningitis cases in a larger area,

preferably country-wide. Cohort analysis will measure vaccine effectiveness as the reduction in incidence of disease attributable to vaccination, using the formula $VE (\%) = (1 - ARV/ARU) \times 100$, where VE is vaccine efficacy, ARU is attack rate in the unvaccinated persons, and ARV is attack rate in the vaccinated persons (25). This analysis will allow a second estimate of vaccine effectiveness and also additional data on impact of the vaccine on rates of bacterial meningitis and on occurrence and magnitude of epidemics, and an estimate of herd immunity. For such an analysis to succeed, retrospective surveillance will be essential to provide pre-vaccination-baseline data of epidemiology, such as previous epidemics of meningococcal disease, endemic rates of disease, and laboratory-confirmation of suspected meningitis cases. Prospective surveillance for clinically-suspected meningitis will then be used for detecting changes in suspected meningitis cases, deaths, and incidence rates of disease. This information will complement data on vaccine coverage, obtained through coverage surveys. Surveillance will focus on clinically-suspected meningitis, using standard case definitions of clinical meningitis validated by WHO in previous vaccine studies (59,60). A clinical definition will be primarily used since intensive laboratory surveillance will be very difficult to implement country-wide. However, for areas with good laboratory surveillance, trends in laboratory-confirmed serogroup A meningococcal disease will also be monitored. The surveillance system will collect information necessary to determine demographics, clinical presentation and outcome, and vaccination status (e.g. vaccine received, vaccination card, and registry confirmation). When available, laboratory-confirmation information will also be collected. Evaluation of attack rates for the vaccinated and unvaccinated persons will allow estimation of vaccine effectiveness for clinically-suspected meningitis and herd immunity; incidence rates of pre- and post-vaccination will allow estimation of the impact of vaccine on epidemics (25).

Special studies

A series of special studies will be implemented to provide additional information on vaccine, including carriage and seroprevalence studies, vaccine-safety evaluations, vaccine-coverage surveys, and studies of prevention effectiveness. Other studies may include evaluation of risk factors for non-vaccination and assessment of acceptability of vaccination.

One of the most important attributes expected from serogroup A conjugate vaccines is their ability to prevent acquisition of carriage, resulting in herd immunity, through reduction in exposure among unvaccinated persons and reduction of disease incidence among non-vaccinated persons. Evaluation of the impact of a Men A conjugate vaccine on carriage and immune response will be essential for taking decisions about introduction of vaccines and development of vaccination programmes. Carriage studies will allow monitoring of possible emergence of other meningococcal serogroups circulating in the population and the potential for serogroup replacement by vaccine escape variants or other virulent strains as has been observed with new pneumococcal conjugate vaccines (56). For these reasons, a series of oropharyngeal carriage and seroprevalence surveys will be conducted in the districts selected for intensive laboratory-based surveillance, before and after immunization with Men A conjugate vaccine. Seroprevalence studies will also allow measuring possible existing natural immunity by serogroup A meningococci acquired prior to vaccination campaigns, especially in the event of recent epidemics of meningococcal disease in the area.

Quality of vaccine product, safety of injections and vaccine-delivery systems, management of sharps and waste disposal, and monitoring of adverse events following vaccination with a Men A conjugate vaccine will be evaluated through passive surveillance, if possible, conducted country-wide. A system for voluntary reporting of adverse events will be set in place to detect severe or fatal events and unusual clinical responses. Because the true rate of adverse events is likely to be considerably underestimated using this approach, additional targeted studies of specific adverse events may be conducted as case-control or retrospective exposure cohorts linked to historical controls. Cross-sectional surveys of vaccine coverage using the widely-accepted WHO sampling methodology will be conducted to allow identification of overall population estimates of immunization coverage using cluster surveys or the Lot Quality Assessment Sampling (LQAS) (57). Prevention-effectiveness studies involve the systematic assessment of the effect of public-health policies, programmes, and practices on health costs and outcomes. Evaluation of the introduction of the Men A conjugate vaccine, implementation of vaccination campaigns, impact of vaccine on morbidity and mortality, and costs and benefits associated with vaccination will allow identification,

assessment, and optimization of possible strategies. This will be done through a series of prevention-effectiveness studies assessing the different possible approaches for the introduction of vaccines, e.g. programme design and implementation process, evaluating potential effects of vaccination on national immunization programmes, e.g. impact on delivery of other vaccines, coordination with other vaccination campaigns, and use of cold-chain systems, and economic analyses.

CONCLUSION

The use of serological criteria for the evaluation and licensure of new meningococcal conjugate vaccines has opened a new perspective in the field of vaccine evaluation. This new approach will facilitate the introduction of serogroup A meningococcal conjugate vaccines in Africa. Under this licensure approach, field demonstration of the effectiveness of new meningococcal conjugate vaccines will be a critical phase in the evaluation of vaccines. Demonstration projects will constitute an important bridge between pre-licensure trials and post-licensure use and wide acceptance of new meningococcal vaccines by national and regional authorities. Special studies, including those on carriage and seroprevalence, safety, vaccine coverage, and prevention effectiveness, will also have a great impact in determining the most appropriate use of the vaccines as part of national immunization programmes. Data from demonstration projects on the Hib conjugate and serogroup C meningococcal conjugate vaccines show their impact on prevalence, carriage, and herd immunity, and also importance of these types of studies. We anticipate that the studies outlined here will similarly demonstrate the dramatic impact of a Men A conjugate vaccine in Africa, an essential step to widespread implementation and elimination of meningococcal epidemics.

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