Abstract

Epidemic meningococcal meningitis is an important public health problem in sub-Saharan Africa. Current control measures rely on reactive immunizations with polysaccharide (PS) vaccines that do not induce herd immunity and are of limited effectiveness in those under 2 years of age. Conversely, polysaccharide conjugate vaccines are effective in infants and have consistently shown an important effect on decreasing carriage, two characteristics that facilitate disease control. In 2001 the Meningitis Vaccine Project (MVP) was created as a partnership between PATH and the World Health Organization (WHO) with the goal of eliminating meningococcal epidemics in Africa through the development, licensure, introduction, and widespread use of conjugate meningococcal vaccines. Since group A Neisseria meningitidis (N. meningitidis) is the dominant pathogen causing epidemic meningitis in Africa MVP is developing an affordable (US$ 0.40 per dose) meningococcal A (Men A) conjugate vaccine through an innovative international partnership that saw transfer of a conjugation and fermentation technology to a developing country vaccine manufacturer. A Phase 1 study of the vaccine in India has shown that the product is safe and immunogenic. Phase 2 studies have begun in Africa, and a large demonstration study of the conjugate vaccine is envisioned for 2008–2009. After extensive consultations with African public health officials a vaccine introduction plan has been developed that includes introduction of the Men A conjugate vaccine into standard Expanded Programme on Immunization (EPI) schedules but also emphasizes mass vaccination of 1–29 years old to induce herd immunity, a strategy that has been shown to be highly effective when the meningococcal C (Men C) conjugate vaccine was introduced in several European countries. The MVP model is a clear example of the usefulness of a “push mechanism” to finance the development of a needed vaccine for the developing world.

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1. Introduction

In 1963 Lapeyssonnie first described the African “meningitis belt,” a vast area that stretches from Senegal to Ethiopia with a 2005 estimated population of more than 300 million where major epidemics of meningococcal meningitis regularly occur [1]. He emphasized the striking periodicity of meningitis epidemics; they start at the beginning of the dry season in late December, peak towards the end of the dry season, and promptly stop with the first rains in May and June. The epidemic season is characterized climatically by the “harmattan,” a hot dry wind that generates a great deal of dust [2]. Most countries in the meningitis belt have had large outbreaks every 5–12 years since the 1940s, but over the last two decades the intervals between epidemics have become more irregular. Furthermore, the belt is expanding further south with meningitis epidemics reported in Burundi, Rwanda, Angola, and Zambia. In major African epidemics, incidence rates can soar to 500 cases per 100,000 population, but in smaller loci disease rates are often greater than 1%. Over the last decade over 700,000 cases in Africa have been reported, and in 1996 there were over 200,000 cases and over 20,000 deaths [3].

Despite antimicrobial therapy, about 10% of cases of meningitis die, typically within 24–48 h after the onset of symptoms. Another 10–20% of survivors are left with major neurologic sequelae such as mental retardation, hearing loss, and seizures [4]. Because about half of the cases during epidemics are working age adolescents and young adults the
disruption and chaos in the community are enormous, and epidemics can quickly evolve into a social, human, and economic disaster for an affected country.

2. Control measures for epidemic meningitis in sub-Saharan Africa

The current WHO approach for control of meningitis epidemics in sub-Saharan Africa is based on early detection of cases and emergency mass vaccination of the population at risk with meningococcal polysaccharide (PS) vaccines [5]. Meningococcal PS vaccines have been available for more than 20 years and have been shown to be effective in preventing disease in adults and older children. Nonetheless, meningococcal PS vaccines have important limitations; they have limited efficacy in infants and young children [6], do not decrease carriage, and do not confer herd immunity [7]. Two meningococcal PS vaccines are available for reactive campaigns in the African meningitis belt: a bivalent A/C PS vaccine for US$ 0.66 per dose, and a trivalent A/C/W135 PS vaccine at about US$ 1.30 per dose. A tetravalent A/C/Y/W135 PS vaccine is licensed but its high cost precludes widespread use in Africa for epidemic control.

A successful reactive strategy depends on good surveillance, accurate bacteriologic diagnosis, availability of PS vaccine, and a logistic system capable of rapidly mounting immunization campaigns. Despite organizational and logistic improvements in recent years African public health officials have been frustrated with having to respond to meningococcal epidemics with strategies that are at best, moderately useful and at worst, ineffective.

3. Meningococcal conjugate vaccines

In the late 1980s, Schneerson et al. revolutionized the field of polysaccharide vaccines by developing conjugate polysaccharide vaccines [8]. By linking carbohydrate antigens from Hemophilus influenzae (Hib) to proteins they formulated a new vaccine that was much more immunogenic than its plain polysaccharide precursor. Plain polysaccharide vaccines are B cell-dependent antigens, they are not able to prime immunological memory and are poorly immunogenic in infants and young children, and their protection is short lasting. The coupling of polysaccharides to a carrier protein transforms PS into T cell-dependent antigens that are capable of priming immunological memory and are immunogenic in infants.

Pharmaceutical development of Hib conjugate vaccines followed, and introduction of these conjugate vaccines resulted in a dramatic reduction in cases of invasive Hib disease. Through the 1990s evidence mounted that the use of Hib conjugate vaccine also resulted in dramatic decrease of carriage and a strong herd immunity effect [9]. In addition to Hib conjugate vaccines, this technology has been used to develop conjugate PS vaccines against Streptococcus pneumoniae, N. meningitidis group C, and more recently against N. meningitidis A/C/W/Y.

During the 1990s the United Kingdom experienced an increasing number of cases of meningitis due to group C N. meningitidis. Vaccine manufacturers were asked to develop meningococcal C (Men C) conjugate vaccines, and in November 1999 Men C conjugate vaccines were introduced in the primary immunization schedule with doses at 2, 3, and 4 months, accompanied by a catch-up campaign of two doses for the 5–11 months age group, and a single vaccination for those aged 1–17 years (later extended to 24 years) [10]. An extensive postlicensure evaluation program documented that group C meningococcal conjugate vaccines were safe and had a dramatic impact on serogroup C disease [11]. The vaccine reduced group C nasopharyngeal carriage by 66% in adolescents and resulted in herd immunity with significant and sustained decrease in cases in those not vaccinated [12]. While the long-term effectiveness (beyond 10–15 years) of the meningococcal C conjugate vaccines remains to be seen, we now know that the Men C conjugate vaccines offered individual protection for vaccinees above 2 years for at least 7 years plus strong herd immunity that extended to all age groups for at least that long. A key point that has been learned from these exemplary post-introduction studies is that a single dose of conjugate vaccine in the age group most likely to transmit the organism (1–24 years) blocks colonization and induces herd immunity [13].

4. Developing a Men A conjugate vaccine for Africa: the Meningitis Vaccine Project

MVP grew out of a WHO-sponsored effort to improve the public health response to meningitis outbreaks in Africa after the devastating outbreak in 1996–1997. In early 2000, WHO asked a group of experts to review the epidemiology of meningococcal disease in sub-Saharan Africa, data from clinical trials of polysaccharide and conjugate meningococcal vaccines, and the costs to develop Men A conjugate vaccines for Africa. The expert group concluded that development of a meningococcal A or A/C conjugate vaccine was feasible and offered an attractive strategy for epidemic control and perhaps, elimination of meningococcal disease as a public health problem in Africa [14]. In April 2000, a group of international experts and delegates from African ministries of health endorsed the initiative, and in 2001 the Bill & Melinda Gates Foundation agreed to fund a partnership between WHO and PATH aimed at developing, testing, and licensing meningococcal conjugate vaccines for sub-Saharan Africa.

Throughout the Fall of 2001 and the Spring of 2002 MVP held extensive discussions with African public health officials who emphasized the key importance of a low vaccine price on the ability of African countries to purchase vaccine in a sustainable way. African leaders asked MVP to vigorously explore less expensive products. In view of these concerns,
MVP convened a series of meetings and consultations with WHO, PATH, and pharmaceutical consultants that resulted in an alternative model for the development of a monovalent group A meningococcal conjugate vaccine [15]. MVP would identify the following:

- suppliers of tetanus toxoid and group A polysaccharide, the two main components of the conjugate vaccine;
- a research laboratory that was willing to develop and transfer a conjugation technology;
- a vaccine manufacturer who could accept the technology transfer and was willing to make a conjugate vaccine that would cost less than US$ 0.50 per dose.

After extensive due diligence, MVP identified the following three partners:

- SynCo Bio Partners in Amsterdam, The Netherlands, for supply of meningococcal group A polysaccharide;
- the Center for Biologics Evaluation and Research of the U.S. Food and Drug Administration (CBER/FDA) in Bethesda, Maryland, for development of a conjugation technology for the polysaccharide-tetanus toxoid vaccine;
- the Serum Institute of India Limited (SIIL) in Pune, India, for supply of the tetanus toxoid and manufacturing the Men A conjugate vaccine.

The conjugation technology was transferred to SIIL in December 2003, and in 2004 SIIL prepared test lots and clinical batches of the study vaccine using the CBER/FDA technology. Animal testing, including toxicity, local tolerance, and immunogenicity of the study vaccine, was completed in 2004, and a Phase 1 clinical study of the Men A conjugate vaccine was completed in India in December 2005. Results of the Phase 1 study showed that the Men A conjugate was safe and immunogenic, and a full report describing these results is included in this supplement [16]. Phase 2 studies in Mali and The Gambia began in 2006, and Indian licensure of the vaccine is expected in 2008–2009. SIIL will produce at least 25 million doses of the Men A conjugate vaccine annually, and the WHO Regional Office for Africa will be responsible for coordinating introduction of the Men A conjugate vaccine through country-wide mass immunization campaigns of people aged 1–29 years with a single dose of Men A conjugate vaccine, as well as a two-dose schedule in under-ones (14 weeks and 9 months). The proposed strategy is expected to induce herd immunity. To document this important point extensive meningococcal carriage studies are planned during a country-wide demonstration study [17]. The enhanced community immunity against group A N. meningitidis will prevent epidemic and endemic disease due to this organism.

5. Future development

Making vaccines is neither easy nor cheap, and vaccine manufacturers must pay attention to profitability if they are to stay in business. Not surprisingly “Big Pharma” companies are more interested in vaccines that have potential markets in developed countries. Therefore, financing the development of new vaccines that are to be used almost exclusively in developing countries, like a Men A conjugate vaccine, is no simple matter. A “push” financing strategy to develop new vaccines involves the provision of financial resources to aid in the pharmaceutical development and clinical testing of products that by themselves would not be developed for commercial reasons. “Push” funds significantly lower the risk to a vaccine manufacturer, and in exchange, a negotiated price for the product may be possible. Achieving this goal immeasurably facilitates planning for the introduction of a product because the price is known up front. The development of the Men A conjugate vaccine is a good example of the usefulness of “push” whereby a needed conjugate vaccine that was of limited interest to large vaccine manufacturers is now being developed [15].

In addition, the vaccine manufacturing field has changed dramatically over the last 20 years. Developing country vaccine manufacturers – so-called emerging suppliers – now make and sell most of the basic Expanded Program on Immunization (EPI) vaccines (diphtheria/tetanus/pertussis, tetanus toxoid, measles, measles/rubella, BCG, and oral polio vaccine) that are used globally. Several of these new suppliers have continued to invest heavily to improve their plants, their quality control, and their clinical programs. WHO prequalification of these vaccines has offered a mechanism that not only establishes a quality standard but also guarantees these manufacturers access to UNICEF tenders. As a group these developing country vaccine manufacturers are interested in filling a niche—that is, making and selling affordable and needed vaccines for developing countries. The success of the Serum Institute of India Limited in being able to accept technology transfer and to produce a Men A conjugate vaccine that meets every international standard and yet remains affordable, offers an attractive model for the development of other needed vaccines. As developing country manufacturers (“emerging suppliers”) master conjugation technology, it will be easier to develop other conjugate vaccines. Because widespread use of conjugate vaccines has been shown to generate dramatic reductions in morbidity and mortality it is important that development timelines are shortened so that needed conjugate vaccines can be made available at prices that developing countries can afford to pay.

References


