The Role of CBER in the Success against Epidemic Meningitis in Africa

The responsibilities of the Center for Biologics Evaluation and Research (CBER) repeatedly draw it into global battles against infectious diseases, such as HIV/AIDS, influenza, malaria, and pneumonia. A particularly dramatic example of the center's contribution to global public health work is the critical role CBER played in developing the technology needed to manufacture a safe and effective vaccine against epidemic meningococcal meningitis at an affordable cost for African countries, such as Burkina Faso, Chad, Ethiopia, and Niger.

The African Meningitis Belt

A hot, dusty wind starts blowing each December or January in Burkina Faso, signaling the onset of the dry season and the yearly outbreak of meningococcal meningitis. The wind, called the harmattan, disappears at the start of the rainy season--usually May—leaving behind illness, death and social disruption. Every 10 to 15 years, the outbreak sweeps across the whole of sub-Saharan Africa from Senegal in the west to Ethiopia in the east, causing even more illness and death.

Virtually all the meningococcal disease of the meningitis belt is caused by *Neisseria meningitidis* serogroup A, although only a small portion of circulating strains is highly virulent (Frasch, 2005). Antimicrobial therapy fails to save about 10% of the victims, while 10 to 20% of survivors develop mental retardation, hearing loss, or seizures. (Préziosi, 2007).

Major epidemics in the meningitis belt have infection rates ranging from 100 to 800 per 100,000 population (Frasch, 2005). Burkina Faso, Chad, Ethiopia, and Niger have been the most affected countries, with 65% of total reported cases in 2002 occurring in those countries (Frasch, 2005).

The largest outbreak of epidemic meningitis in this region occurred in 1996-97, when meningococcal meningitis struck 250,000 people in ten countries, causing 25,000 deaths (Kaiser, 2009). In 2009, another terrible meningitis epidemic swept through Nigeria and Niger, striking at least 25,000 by April and killing at least 1500 in Nigeria alone (Roberts, 2009).

The Meningitis Belt of Sub-Saharan Africa

The meningitis belt of Africa stretches from Senegal in the west to Ethiopia in the east. An estimated 300 million people live in this area, where focal epidemics occur yearly during the dry, dusty season from January to May. Major outbreaks of meningitis sweep across the belt every 10 to 15 years, with attack rates varying from 100 to 800 per 100,000. The most affected countries are Burkina Faso, Ethiopia, and Niger. The meningitis belt appears to be extending southward.

CDC

Despite the long, tragic history of meningitis epidemics, when and where in the meningitis belt the epidemic will hit and how severe it will be remains a mystery. Therefore, WHO customarily recommended the use of an existing polysaccharide (PS) vaccine when the epidemic struck.

Vaccination offered the best chance to avoid the disease: only individuals who lack bactericidal antibodies against the circulating virulent strain develop meningitis (Frasch, 2005). However, mass vaccination with the PS vaccine in the meningitis belt is impractical or of limited use for several reasons: 1) vaccination is usually started too late because of the obstacles in this region to allocating vaccine supplies and logistic resources faster than the spread of the epidemic; 2) mass vaccinations implemented on short notice often disrupt routine health programs, including other immunization programs; 3) PS vaccines offer limited protection to infants and young children; 4) PS vaccines do not confer T cell dependent immunity, limiting the duration of protection; and 5) PS vaccine neither decreases carriage nor confers herd immunity (Préziosi et al., 2007; Twumasi et al., 1995).

An Expanding Meningitis Belt Threatens More Countries

In Africa, most meningococcal disease is caused by the group A meningoccus, and about half of its victims are working-age adolescents and young adults. These meningococcal epidemics cost more than lives and scarce public health funding. The debilitation and killing of so many working age adolescents and young adults causes very significant human, social, and economic losses to the affected communities. A single case of meningitis can drive a family into poverty (Roberts, 2008).

The result is social and economic disaster in these sub-Saharan countries (Préziosi, 2007). As Dr. William Perea, a WHO meningitis expert, explained it to a reporter, "For those four or five months, health workers have to abandon everything else and just deal with meningitis patients" (Cheng, 2010).

The situation might even be worsening: the meningitis belt appears to be expanding further south. Burundi, Rwanda, Angola, and Zambia have also reportedly suffered epidemics (Préziosi, 2007), threatening wider regional social and economic disruption in this part of the world.

A New Strategy: Meningitis Vaccine Project

Public health officials in Africa, WHO, and elsewhere knew they were using outdated strategy to defeat a formidable bacterial enemy. In general, PS vaccines are B cell-dependent antigens and therefore are unable to prime immunological memory. Yet there was already technology available to overcome that problem: conjugate polysaccharide vaccines, pioneered in the 1980s with *Hemophilus influenza* type b vaccine (Schneerson, 1980). Attachment of protein to PS provides T cell epitopes that trigger helper T cells, resulting in both antibodies and memory B cells, even in infants (Frasch, 2005).

But the vaccine that was desperately needed not only had to be safe and effective; it also had to be very inexpensive. Otherwise, countries along the meningitis belt would be unable to afford it and would continue to suffer regularly from recurring epidemics.

In 2000, at the request of WHO, experts studied the feasibility of producing a safe and effective meningococcal vaccine that African states could afford to buy in large quantity. Later that year international experts and delegates from African ministries of health endorsed the initiative. In 2001, the Bill & Melinda Gates Foundation agreed to fund the Meningitis Vaccine Project (MVP)-- a partnership between WHO and PATH, a non-profit organization based in Seattle, WA that works with collaborating groups to provide health care technologies and strategies to areas of the world that have limited resources.

Dr. F. Marc LaForce, took charge of MVP's effort to develop, test, and license a safe, effective, and affordable (less than 50 cents per dose) conjugate vaccine for use in Africa. An official from Niger reinforced the importance of price with the plea to LaForce: "Please don't give us a vaccine that we can't afford. That's worse than no vaccine" (PATH website: http://www.path.org/menafrivac/about-mvp.php). The new vaccine also had to be used as a

preventive strategy, before an epidemic began, in order to reduce disruption of medical care systems and ensure timely protection for the populations.

The problems started early. LaForce couldn't get a major vaccine manufacturer to produce a meningitis A conjugate vaccine for 50 cents or less. So he turned to Serum Institute of India Limited (SIIL) in Pune, which agreed to supply the tetanus toxoid protein that could be conjugated with the polysaccharide, and then make and sell the vaccine to African countries at a deep discount. LaForce recruited SynCo Bio Partners in Amsterdam, The Netherlands, to supply meningococcal group A polysaccharide, and a European research group to develop new conjugation technology and transfer it to SIIL (Préziosi, 2007).

MVP decided to make a monovalent vaccine against group A only, even though a new epidemic strain (W135) had recently emerged (*Weekly Epidemiology Record*, 2002). The decision reflected MVP's determination to keep the vaccine as simple and inexpensive as possible.

The project faced another big challenge in 2003: the research group developing the conjugation technology for MVP announced it would not transfer it to SIIL. LaForce faced the real possibility of failure, and support for the project from colleagues weakened (Roberts, 2008).

That's when CBER stepped in with exactly the right technology at exactly the right price.

CBER Helps Pave the Way for a Desperately Needed Vaccine

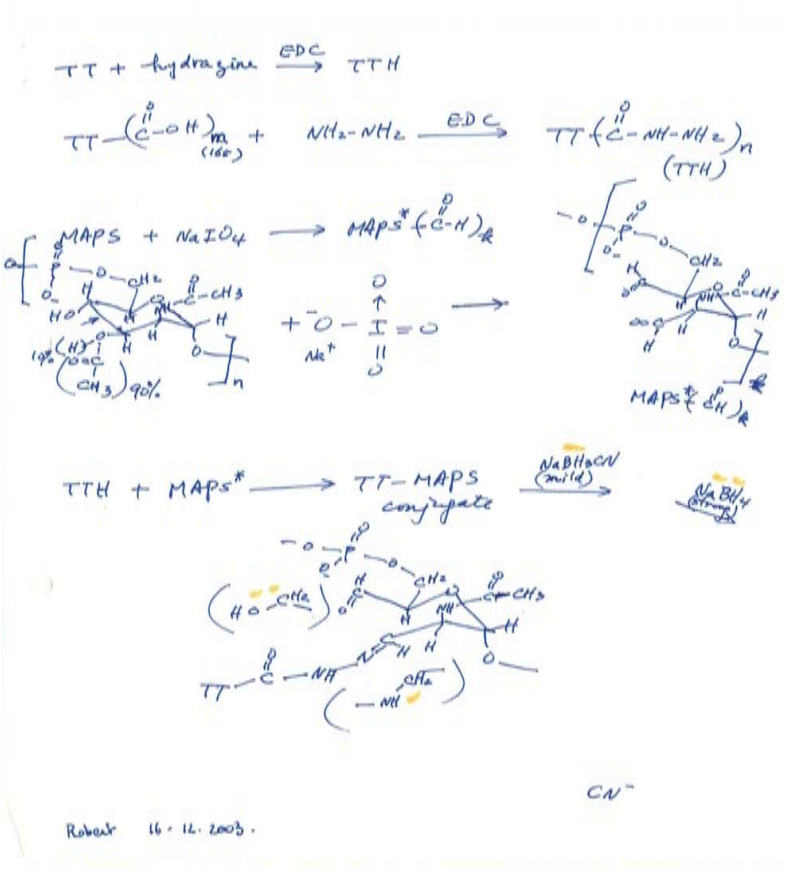
The key to salvaging the MVP lay thousands of miles away at CBER. Robert Lee and Carl E. Frasch, two researchers in the Office of Vaccine Research and Review, had developed a new vaccine conjugation technique, whose details were presented in the patent application the U.S. Public Health Service filed that same year (E-301-2003; "A Rapid High Efficiacy Conjugation Method for Production of Polysaccharide-Protein Conjugate Vaccines").

The Lee/Frasch conjugation method was an improvement over previous techniques. The older methods for making PS-protein conjugate vaccines have low efficiency (about 20%). In addition, the conjugates must be purified to eliminate the unconjugated PS. This inefficiency slows production and raises costs. The CBER technique uses the chemical property of hydrazide groups on one reactant to react with aldehyde groups or cyanate esters on the other reactant. This improves conjugate yield to at least 60%. This efficiency eliminates the need for complex purification; rather, a simple filtration to remove the by-products is sufficient. Thus, the CBER technique substantially increases yield while keeping costs low.

Through a technology transfer agreement, CBER provided the new conjugation technology to MVP via PATH with help from the National Institutes of Health (PATH website: http://www.path.org/menafrivac/product-development.php).

The contributions of CBER didn't end there. The center also developed reagents for evaluating the performance and safety of the vaccine and developed methods to monitor the manufacturing process.

The Lee/Frasch Conjugation Method
2003
Signed by Robert Lee



Courtesy, Robert Lee/CBER

Tech transfer became more personal in December 2003 when two SIIL scientists came to the laboratory of Lee and Frasch at CBER to work for three weeks learning the conjugation method, duplicating the process at a laboratory scale, and receiving standard operating procedures for the conjugation method process and analytic methods. The visiting scientists learned how to activate the tetanus toxoid and meningitis A PS (Men A PS) and then conjugate them; they also learned how to characterize activated tetanus toxoid, activated Men A PS, and the toxoid-Men A PS product.

In February 2004 CBER scientists visited SIIL to provide technical support. Before spring, SIIL sent three lots of Men A conjugate vaccine for testing to the United Kingdom's National Institute

of Biological Standards and Control, which produces many of WHO's international standards for biological products.

The Personal Side of Tech Transfer: Teaching and Training

Carl Frasch (top photo far left) and Robert Lee (bottom photo, second from left) hosted SIIL scientists in December 2003 to teach them the critical laboratory techniques for making the new meningitis A conjugate vaccine. (Photos courtesy of WHO)

The Men A PS Vaccine Becomes MenAfriVac™

Synco BioPartners complemented the CBER transfers, providing SIIL with technology for fermentation and purification of Men A bacteria, preparation of bacteria master and working cell banks, and production and purification of Men A polysaccharide.

Once the product was in hand, the project moved along quickly. Preclinical studies (toxicity, local tolerance, immunogenicity) were completed in 2004. A series of clinical trials followed, starting with Phase 1 in India and a series of Phase 2 and 3 trials in both India and countries in Africa's meningitis belt (http://www.meningvax.org/clinical.php).

In December 2009, the Drugs Controller General of India licensed the new vaccine, now called MenAfriVac. And by June 2010, WHO had prequalified the vaccine. Its cost: 40 cents per dose.

(Prequalification is a service provided by WHO to ensure that vaccines they purchase for use in global immunization programs are safe, efficacious and of good quality.)

Following development of the vaccine, CBER scientists Margaret Bash and Brian Mocca collaborated with researchers from Africa, MVP, PATH, and WHO, who performed on-site clinical studies of the effectiveness of the vaccine among individuals living in the meningitis belt of Africa. The team used a test called serum bactericidal activity (SBA) to compare the level of immune response to the MVP vaccine in one group with that of another group that received a meningitis vaccine that was already in use. The superior performance of the new, MVP vaccine in the CBER SBA test supported the results of other tests conducted by the US Center for Disease Control and Prevention and the Health Protection Agency of the United Kingdom, and thus led to large-scale use of it in the meningitis belt. The CBER researchers presented this information at professional meetings in Alberta, Canada (17th International Pathogenic Neisseria Conference (Sept. 2010) and the Infectious Disease Society of America, 48th annual meeting in Vacouver, BC, Canada (Oct. 2010).

"These guys are heroes."

Early in December 2010 MVP began its first major battle against the scourge of the meningitis belt, launching a vaccination campaign aimed at protecting millions of people in West Africa. The campaign started in Burkina Faso and moved on to Mali, and Niger.

On December 4, 2010, *The New York Times* ran a story with the headline: “New Meningitis Vaccine Brings Hope of Taming a Ravaging Illness in Africa.” The story quoted experts as saying that MenAfricVac is a “milestone in developing inexpensive vaccines against neglected diseases that afflict poor countries.” The article, which noted the invaluable contribution of CBER, also quoted Dr. William Schaffner, chairman of the department of preventive medicine at Vanderbilt Medical School (who was not involved in the project) as saying: “Doing this outside of big pharma and developing the vaccine explicitly for the developing world is very innovative.”

The December 10, 2010 issue of *Science* carried a story in its News of the Week section that carried the following headline: “The Beginning of the End for Africa’s Devastating Meningitis Outbreaks?” The article not only heralded the success of MenAfriVac, but also quoted Chris Elias, president of PATH as noting that the project was, “a model for delivering all sorts of public health interventions, not just vaccines, to poor countries.” That concept wasn’t lost on the Gates Foundation, which is now investing in a pneumococcal vaccine that SIIL is developing (Roberts, 2010).

September 2010. A woman in Mali receives MenAfriVac in an early introduction in preparation for the official vaccine program launch in December. Photo: WHO/Mali

WHO noted that the MVP's work also helped to strengthen systems in Africa for disease surveillance, clinical development of therapies, pharmacovigilance, and vaccine logistics for epidemics in general (WHO, 2010). Honing these public health strategies is of increasing importance during an era in which infectious disease threats have implications for national and global security (Heymann, 2003). Heymann noted the threat posed by emerging and re-emerging diseases to national security of individual countries as well as the potential threat to other countries given the ability of populations to migrate. Indeed, he described the emergence in Africa of the new W135 strain of epidemic meningitis as, "defying emergency preparedness in the form of stockpiled vaccines against conventional strains."

On December 5, 2011 the MVP web site announced that Cameroon, Chad, and Nigeria would introduce the vaccine to 22 million people between the ages of 1 and 29. By the end of December 2011, about 55 million people will have been vaccinated with MenAfriVac over 2010 and 2011.

This effort by FDA to address a major health care project in Africa reflects the agency's recognition that protecting human health globally is linked to its effort to protect human health in the United States.

MVP owes this success to the skills and dedication of many people around the world. The credit to CBER specifically was noted in various publications and web sites. But the contribution of CBER researchers Carl Frasch and Robert Lee was perhaps best summed up (Roberts, 2008) by MVP director Marc LaForce in a news story about their timely contribution of the conjugation technology that enabled the development of MenAfriVac at a price that Africa could afford: "These guys are heroes."

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