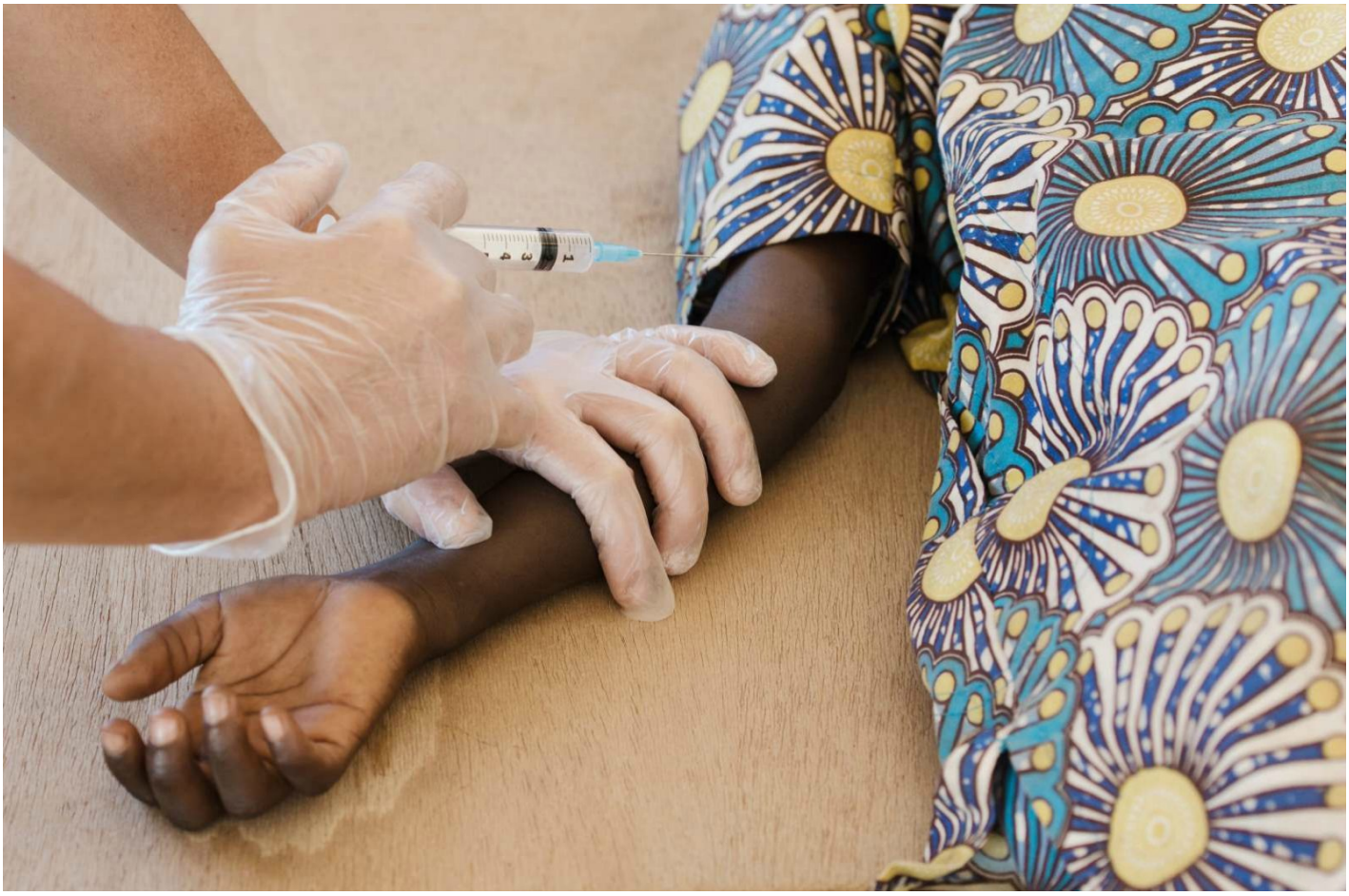
A Novel Partnership Tackles Meningitis

National Institutes of Health (NIH)



In the middle of 2003, Marc LaForce was having trouble sleeping. As the director of the Meningitis Vaccine Project (MVP), he was missing a vital piece of a difficult puzzle. The MVP sought to commercialize a vaccine that would help prevent Africa's devastating epidemics of meningococcal meningitis, a bacterial infection of the brain and spinal cord. The largest documented outbreak, in 1996, sickened 250,000 people in Africa and caused 25,000 deaths. In 2002, a single West African country (Burkina Faso) had 13,000 meningitis cases and at least 1,500 deaths.

To succeed, the MVP needed a vaccine production method with two essential qualities: very effective and very affordable. But in mid-2003, that search hit a dead end. "All projects have their ups and downs," says LaForce, M.D. "We were in the downest of downs."

Then, in June 2003, LaForce had a pivotal conversation with Carl Frasch, Ph.D., a Food and Drug Administration (FDA) researcher. Frasch offered a new method for vaccine production developed by one of his colleagues, Robert Lee. It

ultimately led to an unconventional licensing arrangement. The National Institutes of Health (NIH)—FDA's sister agency, responsible for FDA's technology transfer—didn't license the production method to a company. Instead, it transferred the technology to PATH, one of the nonprofit organizations that collaborated on the MVP. The result would be a vaccine—MenAfriVac—that could dramatically reduce the meningitis rate in Africa. What's more, the product-development partnership that emerged could serve as a collaboration model for effectively tackling other public health issues in developing nations.

Debilitating Effects on Patients and Communities

The quest for a better, affordable vaccine began in 2001 with a $70 million grant from the Bill and Melinda Gates Foundation. That funded the creation of the MVP — a partnership between the World Health Organization and PATH, a Seattle, Wash., nonprofit with a public health focus. The MVP's goal was no small matter, considering the meningitis epidemics that had plagued Africa for decades. The hardest-hit area is known as the African Meningitis Belt, consisting of about 20 countries stretching across the top of sub-Saharan Africa. From 1991 to 2010, nearly 1 million meningitis cases were reported in that area, along with about 100,000 deaths. Other parts of the world did not have the same grim figures. In the United States, for example, there were about 3,200 cases reported from 1998 to 2007, with less than 500 deaths from the disease.

Even when patients receive early diagnosis and treatment for meningitis, a full recovery is not guaranteed. As many as 10 percent of patients do not survive, and up to 20 percent of those who do survive are left with hearing loss, learning disabilities, or brain damage.

In sub-Saharan African, meningitis is particularly debilitating, even beyond the individuals it infects. That's because meningitis tends to strike people age 30 and younger, who are often a household's main wage-earner. Says Steven Ferguson, deputy director, licensing and entrepreneurship at the NIH's Office of Technology Transfer: "The disease is quite significant, not only in terms of mortality, but also the economic impact for the patients and their families."

Veering From the Traditional Licensing Path

Vaccines have been available in the African Meningitis Belt for more than 30 years, but they typically provided short-term immunity that sometimes only lasted for several months, and did not help children younger than 2 years old. The MVP wanted to improve this by providing a conjugate vaccine, a particular type of vaccine proven to be more effective. Originally developed by NIH scientists, conjugate vaccines take a polysaccharide molecule from the outer layer of a disease-causing bacteria (in this case,the group A meningococcal bacterium), and attach it to a "carrier" protein. This boosts immunity to the pathogen, helping the immune system to swiftly attack the pathogen even if it invades several years later.

At the project's outset, LaForce and WHO staff visited Africa to talk with public health officials there. It soon became clear that a more-effective vaccine would not be enough. It had to be affordable — and to African public health officials, that meant a conjugate vaccine costing no more than 50 cents a dose.

It was an audacious goal. In the United States, for example, conjugate vaccines often cost $150 or more, says LaForce.

A Game-Changing Conversation

In early 2003, the MVP leadership thought they had lined up a partnership with a lab that would transfer a conjugation method for the vaccine. But, as LaForce puts it, "It was an arrangement that did not work out." That left the MVP in a precarious spot. In June 2003, LaForce stood in front of a WHO panel in Geneva and informed them that the $70 million

project still had no conjugation method. At that moment, the vaccine project did not exactly seem poised for success.

But before he left, LaForce met someone who also happened to be visiting Geneva: Carl Frasch, Ph.D., chief, Laboratory of Polysaccharides, Division of Bacterial Products at the FDA's Center for Biologics Evaluation and Research. LaForce described his predicament, and Frasch told him about a scientist in his lab, Robert Lee, Ph.D., who had developed a new conjugation method. “He said, ‘Why don’t you come and see us?’” says LaForce. "It was a game-changer." Three days later, LaForce was in Washington, D. C., at the FDA, marveling at what the researchers had developed.

The chemistry used in the conjugation method is not new — it is an existing reaction that has been used for other scientific applications since the 1960s, as Lee is quick to point out. But it had not been used for conjugate vaccine production, due to reliability and reproducibility concerns. The major problem was precipitation in the vaccine, which resulted in the formation of unwanted solids.

"I was bothered by that,” says Lee. “But then I thought, ‘Hey, there is no reason why it cannot be overcome.’" After more than a year, Lee solved the precipitation problem by keeping the solution pH between 10 and 11. Lee’s refinements led to an extremely efficient method that aligned perfectly with MVP’s goals. As LaForce points out:

> *If you're going to make vaccine for 250 million people and you're aiming at a cost that's less than 50 cents a dose, you better make sure that the method is one that yields the most product for the amount of raw material that you put in.*
>
> Robert Lee

Conjugation methods for vaccines represent highly prized, highly protected intellectual property for pharmaceutical companies. So when the FDA’s conjugation method was licensed to PATH, one of the two organizations behind MVP, it represented a dramatic turning point for the project.

The nonexclusive license transfer to PATH was handled by NIH’s Office of Technology Transfer, which played a vital role, says LaForce. "When you're developing contracts, they can go on forever," he says. But with the NIH, it only took about four months. “They were enormously helpful in getting this facilitated,” says LaForce, who retired from his MVP director position in 2012. "The whole process moved flawlessly." Conducting these license negotiations on behalf of NIH was Peter Soukas, a technology licensing specialist in the NIH Office of Technology Transfer.

Thanks to the efficient and expedient technology transfer process, the vaccine project finally had the right method, but PATH still needed a manufacturer to produce the vaccine for less than 50 cents per dose. That company turned out to be Serum Institute of India Ltd. (SII), one of the largest suppliers of vaccines globally. SII told LaForce and his colleagues that the company would have to take on significant business risks to manufacture this new vaccine at such a low price. But SII also decided the benefits far outweighed the risks, considering the expertise the company would gain from making this new vaccine and the contribution it would make in solving a substantial public health problem.

As part of the agreement, the FDA shared its conjugate vaccine know-how in a truly collaborative way. Instead of receiving written guidance for the production technique, two scientists came to the FDA lab in December 2003 to gain expertise in person. "For three weeks, we worked side by side, day and night, and produced 12 small vaccine batches," says Lee. "They had never been in the field of conjugated vaccines, so this was a very good head start for them."

A Model to Emulate

After clinical trials demonstrated that the vaccine (named MenAfriVac) was safe and effective, vaccinations began in

Africa in 2010. MenAfriVac quickly delivered on its promise of improved immunity. In 2011, three countries that had been involved in the vaccine's initial rollout — Burkina Faso, Mali, and Niger — had the lowest number of group A meningitis cases ever recorded during an epidemic season.

By the end of 2012, more than 100 million people in Africa had received the vaccine.

Immunity from a single dose is expected to last up to 10 years — compared to previous meningitis vaccines in Africa, where immunity sometimes lasted less than 12 months.

MenAfriVac probably would not have become a 50-cents-per-dose reality without the public-private partnership that unfolded, one that veered from the traditional path of licensing to a pharmaceutical or biotech company. It's a glimpse of the future, one that the NIH wants to facilitate. "This case inspired us to put together a template agreement on our website, so other NGOs [nongovernmental organizations] can see what the general outline would be for an agreement like this," says Ferguson. "That way, they can seriously consider this pathway in terms of meeting their goal as an organization. Particularly for products that don't have an immediate market in Western countries, we have to think differently in terms of commercialization strategies."

To see available technologies from research institutions, click here to visit the AUTM Innovation Marketplace.