



Scientists are drawn to the intellectual challenge of understanding the virus, what part of the virus makes people sick, and what part of the virus induces an immune response.

The University of Pennsylvania's **PAUL A. OFFIT, M.D.** Discusses his Passion for Vaccine Research and his Hopes for Future Development

Internationally renowned vaccines, immunology, and virology expert Paul A. Offit, M.D., has dedicated his career to discovering vaccines to prevent infectious diseases, and is the co-inventor of the rotavirus vaccine, RotaTeq, developed by Merck. A pediatrician, author, and scientific researcher, Dr. Offit remains a passionate advocate for vaccination.

There was an explosion of vaccines in the first half of the 1990s — the rotavirus vaccine, the human papillomavirus vaccine, the meningococcal vaccine, the pneumococcal conjugate vaccine — which represented development programs that were 15 to 20 years old.

Dr. Offit says these programs happened to come to confluence at the same time. And while he doesn't believe another new vaccine will reach the market in the next 10 years, there will be extended recommendations on existing vaccines and more serotypes added to existing vaccines.

THE BUILDING BLOCKS OF A CAREER

Where did your interest in vaccine research begin, and what influences were integral to your career?

Offit: Early on I was involved with a tremendous research community for vaccines. Working in Philadelphia meant I was close to the heart of the vaccine industry — Roche, GlaxoSmithKline, Aventis Pasteur (now Sanofi Pasteur), and Wyeth. I was most inspired by the work I did while at Wistar, where the rabies vaccine had been developed, and while working with Stanley Plotkin at Children's Hospital in Philadelphia. Dr. Plotkin had developed the rubella vaccine, and the director of the Wistar Institute was Hilary Koprowski, M.D., who was the first person to give an oral polio vaccine. It was great to be part of this community.

THEN AND NOW

How do you think the advances in vaccine development of the past would fare in today's climate?

Offit: When Maurice Hilleman, arguably the father of vaccines, swabbed the back of his daughter's throat in 1963 when she had the mumps, it took four years from isolation of the vaccine to a commercial product. This could never happen today, for a number of reasons. The regulatory burden is one reason. There is a greater burden on pharmaceutical companies to prove there aren't adventitious agents and to show that the vaccine vials contain exactly what they are said to contain. The industry is moving toward the notion of trying to rule out rare adverse events pre-licensure.

The second reason is that there is a skewed vision of risk. For example, Wyeth's RotaShield vaccine was pulled off the market in the United States because of a rare intussusception, which is an intestinal blockage, and there was a death related to that vaccine. There were probably about 1 million children immunized, and while the likelihood is greater for children to succumb to the disease than the vaccine, the notion of any kind of adverse event is always a show stopper.

INTO THE FUTURE

What is the potential for vaccine development?

Offit: I don't envision that there will be a new bacterial vaccine approved in the next 10 years. In terms of vaccines for the big diseases of the world — HIV, malaria, and TB — I'm not optimistic. GlaxoSmithKline has some data regarding its malaria vaccine that are promising. I don't think there is a tuberculosis vaccine in development that is better than the BCG vaccine. And Merck's HIV vaccine, V520, just received a devastating blow; trials were discontinued in September 2007. This was bad news; 90% of all funding in HIV vaccines is dedicated to the concept of trying to develop a T-cell vaccine.

Vaccines hit a low point in the late 1990s. In the mid-1950s there were 27 companies that made vaccines; by the early 1980s this number had been reduced to 18, and by the late 1990s, there were only five. Part of the reason for the decrease in the number of vaccine manufacturers can be attributed to mergers. Another contributing factor is that the industry got much better at making other things. Vaccines have a 200-year history, whereas recombinant DNA technology is a phenomenon of the 1970s and 1980s and so the capacity to mass produce single proteins that was a boon for therapeutics didn't really translate to vaccines, with the exception of HPV and Hepatitis B. It's also much more expensive to develop a biological like a vaccine than

CAREER Highlights

Paul A. Offit, M.D., is Chief, Division of Infectious Diseases, The Children's Hospital of Philadelphia; Professor of Pediatrics, and Maurice R. Hilleman Professor of Vaccinology at the University of Pennsylvania School of Medicine; and Professor of Pediatrics. Dr. Offit, co-inventor of the rotavirus vaccine, RotaTeq, is a consultant to Merck, with whom he shares the patent for RotaTeq. He is the author of several books: *Vaccines: What You Should Know*, *Breaking the Antibiotic Habit*, *The Cutter Incident: How America's First Polio Vaccine Led to Today's Growing Vaccine Crisis*, and *Vaccinated: One Man's Quest to Defeat the World's Deadliest Diseases*. He has published more than 120 papers in the areas of rotavirus-specific immune responses and vaccine safety.

it is to develop a small molecule product. And I believe the anti-vaccine movement certainly has had an impact. Companies were being vilified for making life-saving products.

The market began to rebound in 2000 with the approval of Prevnar, Wyeth's pneumococcal conjugate vaccine. Prevnar became the first billion-dollar vaccine and it is on its way to being a \$2 billion vaccine. HPV could be a \$2 billion to \$2.5 billion vaccine. And while these are not in the blockbuster class of a Lipitor, there is still enough money to keep companies interested. I was worried that the five companies would dwindle to four, three, or two, but this hasn't happened. If anything, the Prevnar experience revitalized these companies' interest in making vaccines.

RESEARCH POTENTIAL

What aspect of your work makes you most proud?

Offit: I spent 25 years working on the rotavirus vaccine, RotaTeq, which was developed by Merck. I'm not sure I have another vaccine in me, but what I, and other scientists, are drawn to is the intellectual challenge of understanding the virus, what part of that virus makes people sick, what part of the virus induces an immune response. Then it's about trying to construct, in our case, a combination virus that doesn't include those genes that are going to make proteins that will make one sick, but does include those genes that are going to make proteins that induce an immune response. This was intellectually fun; we worked seven days a week and loved it.

Once we had the strains in hand by the late 1980s, the interest migrated to finding out whether the concept worked in children. Merck committed to moving forward and spent close to \$1 billion in research and development. We were no longer working in the lab where the rules were all very clear. The goal was just to get to the big trial to see whether it worked. Obviously we wanted it to work because of the potential impact, but mostly we wanted to give the vaccine a chance. ♦

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● Amber Runion
INC Research QuickStart Specialist



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