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Pandemic Perspectives: Paul Offit On COVID-19 Vaccine Worries, Country's Worst Biological Disaster, And What Lies Ahead

by Brenda Sandburg

The prominent virologist and vaccine expert talks to the Pink Sheet about how COVID-19 vaccines could change future research, the 'Rosetta Stone' of the polio vaccine tragedy, and the 26-year effort to create a rotavirus vaccine.

In his biography of renowned vaccinologist Maurice Hilleman, Paul Offit describes eight doors opened by previous scientific discoveries that enabled Hilleman to develop the mumps vaccine. He now sees the opening of another door with the creation of COVID-19 vaccines: the administration of vaccines to pregnant women.

[Pfizer Inc./BioNTech SE](#) and [Moderna, Inc.](#) excluded pregnant women from their COVID-19 vaccine clinical trials, as is always done in vaccine trials. And given the lack of data, the Centers for Disease Control and Prevention usually contraindicates use of vaccines in pregnant women.

But in the case of COVID-19, CDC said a pregnant woman could choose to get a vaccine.

Pandemic Perspectives

One year on from the World Health Organization declaring COVID-19 a global pandemic on 11 March 2020, editors across Informa Pharma Intelligence publications are taking a [closer look](#) at its impact and possible lasting implications for the biopharma and medtech industries.

"So you're about to have a lot of data of an mRNA vaccine in pregnant women," Offit said. "I think that's going to open a door for the other kinds of vaccines that can be given during pregnancy, like a vaccine to prevent respiratory syncytial virus or meningococcus."

Pfizer and BioNTech have gone a step further, announcing on 18 February the launch of a global Phase II/III clinical trial of their COVID-19 vaccine in pregnant women, with the goal of enrolling approximately 4,000 participants.

Offit, director of the Vaccine Education Center and professor of pediatrics in the division of infectious diseases at Children's Hospital of Philadelphia, has a unique perspective on the development of COVID-19 vaccines. A virologist, infectious disease specialist, and co-inventor of a rotavirus vaccine, he is also a member of the US Food and Drug Administration's advisory committee reviewing the data of COVID-19 vaccine candidates.

In an interview with the *Pink Sheet* in mid-February, he talked about hopeful signs of coronavirus immunity following the launch of two vaccines, worries about variants, and significant moments in his career.

Crossing Line With Variants

When the first reports emerged that the novel coronavirus had caused 3,000 deaths in China, Offit was asked in an interview on CNN how bad the virus was going to be. He replied that he couldn't imagine it would be worse than the previous year's flu virus, which had caused about 700,000 hospitalizations and 60,000 deaths in the United States. "I just completely underestimated it," Offit recalled.

The novel coronavirus astounded the scientific community as its wide-ranging assault on the body became known. It causes multisystem inflammatory syndrome in children, affects the ability to taste and smell, has been detected in the brains of people with the virus, and induces an immune response against the lining of blood vessels causing inflammation that leads to strokes, heart attacks, liver disease and kidney disease.

"Here you had this difficult to characterize virus, which had caused these clinical changes and pathological changes that no one would have predicted" and you are now using mRNA technology, for which there is no commercial experience, to stop it, he said. "What could possibly go wrong?" People were "just waiting for the next shoe to drop, which hasn't dropped."

The number of cases of COVID-19 infection, hospitalizations and deaths have recently declined. Offit said he thinks this is because about 35% of the population is essentially immune to the virus, as about 80 million to 100 million people have been exposed to the virus and about 10% to 15% of the population has started to receive vaccines.

With the FDA's authorization of two vaccines in December, and a third at the end of February, there is optimism that control of the pandemic is in sight. Even with the emergence of more transmissible and potentially deadlier variants, the ability of vaccines to prevent hospitalization and death in those infected with the South African, Brazilian and UK variants is reassuring.

Offit said the UK variant, while more contagious, is not a problem as it is fully susceptible to vaccine-induced immunity. The South African and Brazilian variants, which are very close together, “are less susceptible to vaccine-induced immunity, but not in a critically important way,” he said. “To me, the line gets crossed” when even if you’re fully immunized or you’ve been naturally infected, you still get hospitalized with one of these variants. But that has not happened yet.

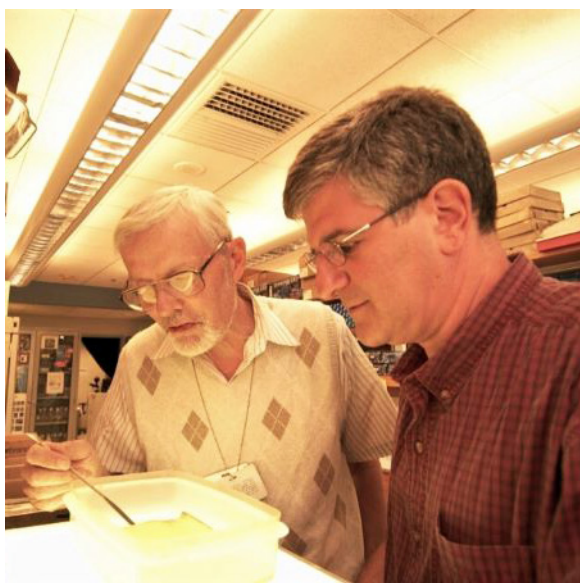
“So for right now, we’re good. And that’s why I think you are seeing the numbers come down,” he said.

Vaccine Production Worry

However, Offit noted there are several things that keep him at night. One concern is that people worldwide are able to get vaccinated. He noted that of 195 countries in the world, about 130 have yet to get one dose of vaccine.

“The critical lesson that has been learned, I’d like to think has been learned, is that what happens in one part of the world affects all parts of the world,” he stated. “We have to put in place a surveillance system so that when a virus like this pops up again, and it will pop up, that we know it immediately, that we respond to it immediately” and start working on a vaccine immediately.

Offit also worries about production of vaccines, wanting it to be done as quickly, efficiently and correctly as possible.



PAUL OFFIT (RIGHT) AND H. FRED CLARK
DEVELOPING ROTAVIRUS VACCINE IN LAB AT

“You don’t want to rush it to the point that in any sense there would be a problem with a batch of vaccine,” he said. “If people are scared about the vaccine, then you’ve lost the one way you have out of this.”

Offit noted that it took FDA a year to validate the manufacturing process for the rotavirus vaccine he co-invented, which was licensed in 2006. The validation period is not as long for COVID-19 vaccines given the urgent need to get them out as quickly as possible.

The five COVID-19 vaccine manufacturers that have started commercial scale manufacturing have faced challenges in scaling up manufacturing to produce hundreds of millions of doses due to limited

CHILDREN'S HOSPITAL OF PHILADELPHIA,
CIRCA 2005 Source: *Courtesy of Children's
Hospital of Philadelphia*

manufacturing capacity. (Also see "[How Operation Warp Speed Helps Clear Obstacles To COVID-19 Vaccine Production](#)" - Pink Sheet, 11 Feb, 2021.)

In an effort to address this problem, Sanofi and Novartis have stepped in to help with production of the Pfizer/BioNTech vaccine. (Also see "[Novartis Steps Up To Plate To Produce Pfizer/BioNTech COVID-19 Vaccine](#)" - Scrip, 29 Jan, 2021.) Sanofi is also providing manufacturing support to J&J for its COVID-19 vaccine, as is [Merck & Co., Inc.](#) (Also see "[Merck's COVID Manufacturing Deal With US Government Goes Well Beyond J&J Vaccine](#)" - Pink Sheet, 2 Mar, 2021.)

Another thing Offit worries about is the anti-vaccine movement and whether it will convince a critical percentage of people not to get vaccinated. Offit is one of the most prominent critics of the movement, writing and speaking extensively about the harms it has caused.

The Rosetta Stone Of The Cutter Incident

On the manufacturing front, the experience with Salk's polio vaccine shows that problems can arise in shifting from making smaller batches of a vaccine to mass production.

Salk's vaccine consisted of killed poliovirus from three poliovirus types that were grown in monkey kidney tissue cultures and inactivated with formaldehyde. Salk provided protocols for developing the vaccine to the five manufacturers that were licensed by the government to make it.

One of the manufacturers, Cutter Laboratories, had trouble inactivating the virus and live virus remained in several of its lots. Soon after the vaccine was sent out, there were reports of children being paralyzed after receiving it. Ultimately, 164 were permanently paralyzed and 10 died.

"It was, I think, the worst biological disaster in this country's history," Offit said.

He was surprised how little information there was about what caused the tragedy and sought to unearth the details. He spent seven years researching and interviewing people who had been involved in the events of the time. Offit said he never got a straight answer from experts he talked to about what happened at Cutter. It wasn't until he went through archival material that he realized it was a scale up incident, that all the companies had problems consistently inactivating the polio virus with formaldehyde, and that Wyeth had also manufactured at least one lot of the vaccine that paralyzed and killed children.

Offit documents what happened in "The Cutter Incident: How America's First Polio Vaccine Led to the Growing Vaccine Crisis." He discovered there was a document called "The Wyeth Problem," that described Wyeth Laboratories' difficulties in making the vaccine. He said this was really "the Rosetta Stone" of the book.

Offit heard about the document, which the CDC had not made public, from the person who wrote it, and he then began looking for it. He was on CDC's Advisory Committee on Immunization Practices at the time and was able to meet with CDC's archivist, who took him to the National Archives and Records Administration branch outside Atlanta. The archivist pulled down an unmarked black-brown box from a shelf "and there it was," Offit recalled.

In one chapter of his book, Offit describes exactly what went wrong that resulted in Cutter lots of the vaccine containing live virus. The first factor was Salk's use of the most deadly strain of type 1 polio in the vaccine. Cutter's choice of filter to remove cells in which the virus was grown allowed virus to remain hidden in the debris. The company also stored the virus too long before it was inactivated and failed to determine how long to treat the virus with formaldehyde. And Cutter did not inform other researchers or the government that it was unable to consistently kill the virus.

Such a situation would be impossible with COVID-19 vaccines as none of them are made with live virus. And vaccines are now closely regulated and must demonstrate lot consistency. However, Cutter's experience shows there are potential hazards in mass production of a vaccine.

26-Year Quest For A Rotavirus Vaccine

Offit knows first-hand how difficult it is to create a vaccine. He worked with Stanley Plotkin and H. Fred Clark to invent a vaccine for rotavirus, a diarrheal disease in infants and young children. It took them 10 years to do the research to create the virus strains, and another 16 years for Merck & Co. to do the research and development that resulted in the RotaTeq vaccine.

There was an earlier vaccine, Wyeth's RotaShield, which was licensed in 1998 and withdrawn from the market the following year due to its association with intussusception, a bowel obstruction. (Also see "[What Came Before COVID-19: Two Centuries Of Vaccine Development](#)" - Pink Sheet, 19 Oct, 2020.)

At the time Offit began working on the rotavirus project, the virus had only recently been found in humans, although it had been known as an animal pathogen for decades. When he, Plotkin, and Clark, a veterinarian, began studying rotavirus they were trying to understand it and were not thinking of making a vaccine, Offit said. He noted that 200 researchers in labs around the world who were also studying the virus would gather together a couple of times a year and share their work.

Major Influencers

Offit, 69, graduated from the University of Maryland School of Medicine and then had an internship and residency in pediatrics at the Children's Hospital of Pittsburgh. He also had a fellowship in infectious diseases at the Children's Hospital of Philadelphia.

One of the most influential people in his life was Ellen Wald, who was an infectious disease specialist at the University of Maryland School of Medicine when he was there and then moved to the Children's Hospital of Pittsburgh. "She was such a clear, thoughtful, brilliant person who just explained things in such a clear manner. She made infectious diseases fun," Offit said. "She's the reason I think I went into infectious disease because she made it so compelling."

Plotkin was also a major influence in his life. The inventor of the rubella vaccine, Plotkin also did seminal work on rabies and anthrax vaccines. "I've never met anybody, I think, that smart. He had a perfect sense of judgment. He just was always right," Offit said.

Maurice Hilleman made a similar impact on Offit. He was the co-inventor or primary developer of nine of the 14 vaccines now given to young children. In his biography of Hilleman, Offit describes him as "the scientist who saved more lives than all other scientists combined."

Labor Of Love

Offit began working on that book, "Vaccinated: One Man's Quest to Defeat the World's Deadliest Diseases," after learning that Hilleman had been diagnosed with cancer and given about six months to live. Hilleman agreed to be interviewed about his life, and Offit met with him several times a week in the months before his death in 2005. Offit tried to record the sessions but Hilleman hated the recorder, so Offit would turn it off and when he went back to his car write down everything he could remember.

"He was such an irascible, brilliant, profane man," Offit said. "I thought, here are all these amazing stories that are going to die with him."

Hilleman worked at Merck & Co. for 27 years where he led vaccine R&D. Offit recounts astonishing events in Hilleman's career, such as his pressuring fellow employees to volunteer to take his hepatitis B vaccine then in development. He also describes how Hilleman discovered the world's first cancer vaccine, which was for chickens, and got Merck to become the world's biggest chicken and egg producer.

The book, which Offit called a labor of love, also gives vivid accounts of the work of other scientists. One chapter, Eight Doors, describes the discoveries that were the foundation for Hilleman's development of the mumps vaccine. One of these findings was that viruses could be grown in animal and human cells in the laboratory instead of in whole animals or chopped-up animal organs. John Enders, Thomas Weller, and Frederick Robbins won the Nobel Prize in Physiology or Medicine in 1954 for discovering how to grow polio virus in tissue cultures.

Like the Cutter Incident, the book provides a riveting narration of vaccine research. The Cutter Incident begins in 1916 with the polio pandemic in New York City and moves through Salk's research, the nation's jubilation when the polio vaccine field trial results were announced, the

meeting at the National Institutes of Health (which was then in charge of vaccine licensing) when scientists and company representatives discussed what to do following reports of paralysis with the vaccine, to the trial against Cutter.

Defining Experiences

The book has personal significance for Offit. When he was five years old, he spent six weeks in a polio ward at the Kernan Hospital for Crippled Children, where he saw children in iron lungs.

Offit was born with clubfoot, which was casted to straighten it. But his right heel did not touch the ground when he walked so his parents took him to see the head of the clubfoot clinic at John Hopkins University, who told his parents that his foot should not be operated on. But Offit's father disagreed and had someone who had recently finished an orthopedic residency do an operation that landed Offit in the hospital. His parents were unable to visit him as his mother was pregnant and had appendicitis, and his father had tried unsuccessfully to sneak in one day and was banned from the hospital.

Offit remembers staring out the window of the front door of the ward, alone with no distractions. When he was in medical school he did a rotation at this hospital and went back to that room. While it had been transformed into an office space, the door was still there with the same molding. He recalled walking over and looking at the door and crying.

"I think the reason I write books about child advocacy, or the reason that I became a pediatrician, the reason that I stick with it, even though I get a lot of hate mail, is that I see children as vulnerable and helpless and alone," Offit said. "I just think that those scars of your childhood become the passions of your adulthood."

Another childhood incident also had a profound impact on him. At the age of five, he fell on a playground and landed on his abdomen. The next day his mother took him to see the family doctor, Milton Markowitz, who was out of town. The physician filling in dismissed Offit's complaint of pain and sent him home. The following day, Markowitz returned to his office, looked through his notes, and called Offit's mother to see if Offit was still in pain. Markowitz then drove to Offit's house, found he had a ruptured spleen, and drove him to the hospital where he had surgery that night.

Offit's remembrances carry the same poignancy as the stories in his books, which describe in captivating detail how vaccines were developed and the triumphs and tribulations of the scientists who built upon each other's work. The history is particularly powerful now as we move through our own public health crisis.

