Paul Offit, MD, on risk and reward in medical innovation

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In today's episode of Moving Medicine, AMA Chief Experience Officer Todd Unger chats with good friend of the show, Paul Offit, MD, the director of the Vaccine Education Center and an attending physician in the Division of Infectious Diseases at Children's Hospital of Philadelphia, about his book: "You Bet Your Life."

Find more information and purchase options for "You Bet Your Life."

Speaker

- Paul Offit, MD, director, Vaccine Education Center; attending physician, Division of Infectious Diseases, Children's Hospital of Philadelphia

Transcript

Unger: Hello, this is the American Medical Association's Moving Medicine video and podcast. Today we're talking with Dr. Paul Offit, the director of the Vaccine Education Center, and an attending physician in the Division of Infectious Diseases at Children's Hospital of Philadelphia, about his new book, You Bet Your Life. I'm Todd Unger, AMA's chief experience officer in Chicago. Dr. Offit, it is great to talk to you. I'm so excited to talk to you about your book because it really is a fascinating look at the failures and tragedies concurrent with medical innovation. I just ... I want to start with a question to you in general, which is, a lot of the conversations that I have over the past two years with physicians have been about reassurance, especially in regard to vaccines. I'm just going to say your book is not necessarily in the same vein as reassurance. I'm curious, why did you feel like now is the right time to undertake that particular message?
**Dr. Offit:** I think it's about asking people to have realistic expectations when there's a medical innovation. I mean, I'm on the FDA's Vaccine Advisory Committee. I have been for four years, and when, for example, in December 2020, we sat down to make a decision about Pfizer's vaccine or Moderna's vaccine, we were being asked to make a decision about vaccines for hundreds of millions of people based on studies in 20 or 50,000, 15,000 people, right? Pfizer, 20,000 people got a vaccine. Moderna up to 15,000 people got a vaccine. Always, always in the historically, with regard to medical innovations, there is a problem. You learn as you go. There is invariably a human price paid for innovation. We knew nothing about mRNA vaccines. This was a novel technology, and so the question was, when was the other shoe going to drop? How bad was that problem going to be, and how rare was it going to be?

It ended up being actually remarkably rare. The mRNA vaccines are a rare cause of myocarditis, inflammation of the heart muscle. The vectored virus vaccines like Johnson & Johnson or AstraZeneca, are a very rare cause of these blood clots. Now, myocarditis and blood clots are caused by the disease at a far more common rate. I just, I just was, I guess, worried that when people would see that they would go, "Well, shouldn't we have known this? Shouldn't we have known this beforehand?" Because it's never true. You're never so sophisticated in science or medicine, at least not to this point, that you're not going to find out something that surprises you and both of those things surprised us.

**Unger:** Do you think that people's expectations around risk of have gotten out of whack, relative to past medical innovations?

**Dr. Offit:** I think people don't understand risk. I think that they tend to overrate risks from something that you do. So, for example, if you give yourself or you give your child a vaccine and there is a risk associated with that, they rate that much higher than a risk say of not giving the vaccine, and then having the disease. I mean, there are no risk-free choices. There are just choices to take different risks. So, the goal is always to take a lesser risk, and I think that when people, for example, think, well, I'm just not going to get this vaccine, then that's they think that's a risk-free choice but it's not.

In the case of COVID, for example, you're far more likely to suffer myocarditis, far more likely to suffer blood clots for example, if you risk the disease, which is common, than if you choose the vaccine. I think we don't get that. Also, I don't think we numerically ever understand risk. The New York State, for example, sells lottery tickets where you have roughly a 14 million to one chance of winning, with a simple phrase, "It could happen to you." I think that's how people see it.

**Unger:** I think too, just in that calculation, I think they're probably pretty good parameters about what happens if you already get COVID, in terms of those outcomes, vaccinated versus unvaccinated but maybe like people are missing that first one, which is like, what are my odds of getting COVID in the first place? Maybe you can't make that calculation.
Dr. Offit: Yeah, no, I think you're right. I mean, I think people, they, well ... what was I going say? I think, Jon Yewdell, who is the head of the Virus Research Lab at the National Institute of Health, said it best. He said." Over the next few years, you're going to have two choices, which is to get vaccinated or get naturally infected." This is a common, highly-contagious disease, and so that should be the calculation but I don't think people see it that way. I think they live on a lot of denialism. They think "This doesn't happen to me," and then when they see people dying because it's a little hard to ignore the fact that almost a million people have died in this country from this disease, they say, "Well, that person probably just had certain medical problems that put them at risk. That's not me."

Unger: One of the examples that you give, and I think it's a good perspective, is about innovation around the polio vaccine, where there was a great deal that went wrong up front but it evolved into a place where things went right to the point, of course, where we've pretty much eradicated that. What do you lay out, in terms of learnings from that experience, and what have we been able to carry forward from there?

Dr. Offit: You know, I think certainly, when Donald Trump, President, then-President Trump stood up at the rose garden and announced Operation Warp Speed, this massive $10 billion infusion into the COVID vaccine effort, he said, "We haven't seen anything like this since the Manhattan project." Meaning, since that 1942 to 1946 project to make nuclear arsenals, nuclear bombs, but we had the. The thing was, the 1955, 1954 to 1955, that was operation Warp Speed One. What the March of Dimes did was they funded the research. They paid for the big clinical trial, the phase three trial, which normally a company would pay for. They mass produced that vaccine for, they paid for mass production of that vaccine for five companies to do that, even though we didn't know whether the vaccine worked or not. They built the buildings. I mean, they, that was Operation Warp Speed One.

When the trial was announced as being successful, that vaccine was licensed in two and a half hours. So, within a year you had done the major sort of clinical trial, mass produced the vaccine and gotten it out there, and as a consequence, we eliminated polio from this country by the late 1970s. That was Operation Warp Speed One. It tells you what you can do when you put a lot of money into something. But, I think what we learned from that episode also was probably the hardest part of making a vaccine actually is mass producing it. It's easier to make 700 doses in your laboratory than it is to make hundreds of millions of doses and that's where the problem came. There was one of the companies that was a relatively newcomer to vaccine manufacturer was Cutter Laboratories of Berkeley, California. They made that vaccine badly.

They failed to completely inactivate the virus with the chemical formaldehyde. As a consequence, 120,000 children, primarily in the West and Southwest were inoculated with live, dangerous polio virus. About 40,000 developed abortive or short-lived paralysis. 164 children were permanently paralyzed and 10 were killed. I think it was the worst biological disaster in this country's history, and led really, to the birth of vaccine regulation. That was a tragic moment. One other thing about that
moment because it sort of relates to when we are considering vaccines for children, when we considered vaccines for the five to 11-year old, COVID vaccines for the five to 11-year old, that was roughly a 2,400 child trial, roughly. I got a lot of, pretty much hateful email from parents saying, "Really? 2,400 children? That's all you want to look at? Whereas, for the adult's trials for Pfizer's vaccine, you looked at 40,000 people. Why such a small trial?"

Now, in that trial, in that 2,400 trial, which was basically two to one vaccine to placebo, 1,600 children got vaccine. About 800 got placebo. So, in the placebo group, there were 16 cases of COVID. So, 16 children suffered COVID. So, I wrote back to some of these people and I said, okay, "We could do a 24,000 child trial, not a 2,400 child trial and then there wouldn't be 16 cases of COVID. There would be 160 cases of COVID, roughly. So, what price do you want to pay for knowledge? What human price do you want to pay for knowledge?" That related back to the polio vaccine because Jonas Salk didn't want to do that clinical trial. He had tested the vaccine in about 700 children in and around the Pittsburgh area, found that it was safe, found that it induced an immune response, which he thought was going to be protective.

He didn't want to do that trial. He didn't want to give placebos to children first and second graders in the 1950s, knowing that every year 20,000 to 30,000 children would be paralyzed by polio, that 1,500 children would die from polio. But nonetheless, the trial was done. 420,000 children got vaccine. 200,000 children got placebo and they were followed over a year. It was the biggest really medical experiment I think in history, in terms of number of people tested, and the vaccine was deemed safe, potent and effective. So how do we know it was effective? We knew it was effective because 16 children died of polio in that study, all in the placebo group.

We knew it was effective because 36 children were paralyzed in that study, 34 in the placebo group. Those were first and second-graders in the 1950s. I was a first and second-grader in the 1950s. Those children could have lived long, fruitful lives but for the flip of a coin. So, it works both ways. I mean, there is invariably a price paid for knowledge and we have to be willing at some level to accept that price but it's really hard.

**Unger:** Yeah. You point that out that the heartbreak of those particular statistics. I don't think about many people necessarily think about that, when they think about those clinical trials. You also take the readers through a lot of different medical innovations, not just vaccines but blood transfusions, anesthesia, gene therapy, chemotherapy, among others. Obviously, thanks to these medical breakthroughs, the lifespan of Americans has increased by 30 years. That's a huge improvement, yet, all of these different episodes provide lessons about when and how we accept new technologies. Is there ever a time when that risk is too great and what barometer do we use to determine that?

**Dr. Offit:** Right. I mean, it's interesting because the heart transplant story has sort of evolved since I've written the book. But, what I talked about in the book is that there are, if you look at the sort of medical history of heart transplant, it is pretty grim. I mean, we've gotten much better now at heart
transplants, in terms of picking the right kind of immune suppressive agents. But nonetheless, about 4,000 people who are on the heart transplant waiting list, so about 1,300 of whom will die while waiting. So, do you want to take the risk, as I mentioned in this book of getting a pig heart, which would be genetically modified so that you would be less likely to reject it? But, you would be one of the first ones to do that. Well, that just happened, actually, since I wrote the book, at the University of Maryland, there was a pig heart transplant.

There was recently a pig kidney transplant, so we did enter that era. But again, it's actually Christiaan Barnard, who did the first heart transplant on a man named Louis Washkansky, who was dying. He said, "If you come to a lake and it's full of alligators, you're not going to swim across the lake, unless you're chased by a lion. Then, you'll take your chances." That's sort of how he saw that first heart transplant. The man, he believed, had little to lose because he was dying. So, but with regard to now, if you're on the heart transplant waiting list, you know you may be one of those people who dies while waiting. Do you want to take a riskier procedure? There are no risk-free choices.

**Unger:** I love your analogy there, which is like you want cross that bridge or not? If you have a lion chasing you, that does affect your risk perception versus not. You also said in a quote, "In the domain of medical innovation tragedy cannot be prevented no matter how many regulations are put in place, and at the same time, some failures have led to greater oversight." That's clear. How do you find that balance? What role do you see, with oversight, playing in the realm of medical innovation because it's going fast and furious right now, because so much of ... we think about gene therapy and anything beyond that, it's just so new and there are a lot of unknowns.

**Dr. Offit:** No, I think gene therapy is a perfect example of this. Because, one, I'm at the University of Pennsylvania, so that was the first gene therapy death. It was a boy named Jesse Gelsinger, at the time was 19 years of age. Jim Wilson, who was the researcher at the time, sort of slowly went forward to introduce the gene he was lacking, which was ornithine transcarbamylase, which meant he would get a buildup of ammonia in his bloodstream, and occasionally, he would go into a coma when he refused to take the medicines he needed. So, he was one of the first gene transplant recipients. Interestingly, that the vector that was used by Jim Wilson, was a replication defective adenovirus, which is essentially the exact same thing that used in Johnson & Johnson's vaccine or in AstraZeneca's vaccine, which were also replication defective adenoviruses.

They're the gene that's introduced into cells, is the SARS-CoV-2 spike protein. Here for Jesse Gelsinger, was the gene ornithine transcarbamylase. So, Wilson went slowly and then nonetheless, Jesse Gelsinger had essentially a sepsis-like disease, which overwhelmed him and he died. It was only in retrospect, that you realize that he had this massive production of Interleukin 6. So, when that was realized, and then you realize that the people who get CAR T therapy, which is again, a way where you take someone's T-cells out, you re-engineer them, so that they'll kill your cancer cells. Then, that happened with a girl named Emily White, had a five-year old who had an essentially a
resistant leukemia. So, they did CAR-T therapy for her. Then, she started to get the same symptoms of Jesse Gelsinger. They looked, they realized she had the same problem, an increase in Interleukin 6 production.

At the time then, there was a medicine Tocilizumab, which could treat that, so her life was saved. So, she became a success story and so she met President Obama. She was on the Today Show. She's constantly feted and if you go to the CAR T therapy lab, what you see are all pictures of her. Her standing next to Obama, her on Dateline, NBC and NBC, the Today Show. What you don't see is pictures of Jesse Gelsinger but it is people like Jesse Gelsinger who allowed people like Emily Whitehead to live. So, we always are much more comfortable celebrating our successes and not the failures that invariably led to those successes.

But in terms of regulation, when the gene ... when Jesse Gelsinger died, there were many more regulations put in place to try and prevent that from ever happening again. But nonetheless, there was a retrovirus gene that was used by French researchers. It was given to 10 children who had severe combined immunodeficiency disease, and four of those 10 children got leukemia because of that vector, because it sort of inserted itself right in front of a gene that increases your risk of leukemia. So again, you can't regulate away from these kinds of problems. You can't. You always learn as you go. That was the purpose of writing this book, to try and make that point.

**Unger:** You also point out, when something bad does happen, we tend to want to create a narrative where we blame somebody or vilify the innovator. You point out several instances of this, a person that invented the x-ray. One day, you've got statues being built on your honor. The next you're not. Or even Jonas Salk, for what he was able to bring, but then you have a bad outcome due to bad manufacturing. How do you ... this has got to have a chilling effect on of course, your desire to innovate, because there is that risk. How do you inspire innovation for that next generation of physicians, knowing that there are consequences, like you point out?

**Dr. Offit:** We like to believe that there's some way to explain all this, which is to say that there's some way we can control it. So, if we can find, say, look, Jim Wilson, for example, who did that gene therapy, he was the bad guy because he wasn't careful enough, because he may have missed something in the animal model experiments, et cetera, where that wasn't true. I mean, he went slowly and carefully, and just ended up learning something that had to eventually be learned and was. Same thing with Jonas Salk. I mean, he wasn't responsible for mass producing the vaccine, but he certainly, there were certain things that were, regarding testing in those companies that weren't done as well as they could have been done.

But Jonas Salk wasn't easy to blame for the Cutter incident, even though it wasn't his problem. But that gives us some sense of control. See, that's why it happened. That way it won't happen the next time. I think part of the point I'm trying to make in this book is it will happen the next time. You can't regulate away these issues. There's always a learning curve and people will say, "Well, okay, I'll just
wait till the learning curve's over," but it's never over.

Unger: You can tell I'm really excited about this book. I just loved reading it and there's so much to take away from it, which we obviously can't talk about here. Of all the stories that you told, which one stands out to you the most, and stays with you?

Dr. Offit: I think probably the Ryan White story, the blood transfusion story. I mean, he, because just because he was such a brave young man. I mean, here's a boy who had hemophilia, and had hemophilia at a time when HIV first came into this country and contaminated the blood supply. He got HIV from a contaminated lot of blood and he was vilified because at the time, it was believed that this must have meant that he was gay. So, he was ostracized and we were unsure about exactly how HIV was transmitted. So, he was really marginalized. But, he was so brave and straightforward for such a young man. That was an inspiring story to me. There were a lot of inspiring stories in these, in this, as I sort of go through these innovations.

But, I think that, and also, you're never play past the problem with blood transfusions because there can may be new viruses that are introduced into the population or there may be viruses that we don't test for. Anytime you get a whole blood transfusion, you are to some extent taking risks. But the point in medicine is to make sure that the benefits clearly outweigh the risks, even though some of the risks are unknown, which has always been true with blood transfusions. I mean, we used to do, back in the 1600s, they did blood transfusion using farmyard animals. We don't do that anymore but we sort only learned hepatitis B virus entered the blood supply. And probably caused the largest single source outbreak of an infectious disease ever, in terms of bloodborne diseases. So, you learn as you go, always.

Unger: Now, last question. You hear this in regard to many things but this idea, if we don't pay attention and learn from the powerful lessons of the past, then we are condemned to repeat them. What is the one thing that you want readers of your book, and particularly those in the medical profession, to walk away with after reading this book?

Dr. Offit: Right? That fear of an adverse outcome shouldn't stifle innovation. Push forward. Realize that there are going to be problems because there always have been but that shouldn't slow research. We should be made wise by our experiences, not nervous by them.

Unger: Dr. Ofitt, thank you so much. I loved your book. For everybody out there, pick up a copy of You Bet Your Life. It's just a great piece of history, with so many implications for what we've been going through today. Dr. Offit, thanks for being here. Really enjoy talking to you. Make sure you don't miss another great conversation like this. Subscribe to our YouTube channel or check out all our videos and podcasts at ama-assn.org/podcasts. Thanks for joining us today. Please take care.
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