Paul Sax interviews Sam Katz
Measles Vaccine
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Text Intro to Accompany Podcast:

In the first Open Forum: Infectious Diseases podcast, Editor in Chief Paul Sax, MD, interviews Samuel L. Katz, MD – a pediatrician and virologist who played an integral part in the development of the measles vaccine. Dr. Katz discusses the history of measles – and gives his views on how to stop current outbreaks. He is currently the Wilburt Cornell Davison Professor and Chair Emeritus of Pediatrics at Duke University.

Podcast Transcript to Accompany Podcast:

Hello my name is Dr. Paul Sax, and I am Editor in Chief of Open Forum: Infectious Diseases. Today I am delighted to be joined by Dr. Samuel Katz. Dr. Katz is a pediatrician and a virologist whose career has been devoted to vaccine research and development. Today we’re going to talk about some of the activities around development of the measles vaccine.

Sam thanks for joining us.

Let’s start by having you describe the circumstances that allowed you to get involved in vaccine research. This was back in the 1950s?

Yes indeed. I was a pediatric resident at Boston Children’s Hospital in 1955 when Massachusetts had its last big outbreak of Polio. That got me more interested in infectious diseases and viruses in particular. And as a result I ended up in the laboratory of Nobel Laureate John Enders as a research fellow.

Sounds like Dr. Enders was quite a character. Can you describe him a bit for us?

He was an absolutely wonderful mentor and for me absolutely a father figure. He was a guy in a very wealthy family who had been intended to go in the real estate business, but he didn’t like that so he went to graduate school at Harvard to study Ancient Celtic Languages. But fortunately he had a roommate from Australia who was working in Hans Zinser’s lab on Microbiology. He took Enders to visit the lab and that was the big change in his life. He decided to get his doctorate in microbiology, which he did under Zinser, and eventually ended up heading the virus research lab at the Children’s Hospital in Boston.

So what was he like, you said he was a wonderful mentor and how about as a person?

Well he was the kind of person who was modest but very, very knowledgeable. All the time we were working in the lab – with viruses, with cell cultures, with blood specimens, with potential vaccines -- he would give these materials to anyone that visited the lab who was a legitimate investigator. His attitude was the more people working on a problem the more likely you were to have a solution. He shared generously and was an absolutely superb person with whom to interact.
I would say the only funny characteristic was despite coming from a wealthy family, he was a little bit penurious. We were probably the only laboratory in the country that gave money back to NIH at the end of the year instead of spending out the last dollars in one's grant. I don't think NIH knew what to do with that money, but they received it from the Division of Research Infectious Diseases each June.

That's a remarkable story. So your involvement in the Measles Vaccine Project, how did that start?

When I got to the Enders lab they were already working on Measles. They had isolated the first Measles virus from a young man named David Edmonston, who was a schoolboy in the Boston area. That virus had been put into monkeys and shown that in susceptible monkeys it produced fever and rash and viremia. Virus was recoverable from the blood and eventually they developed immunity. So that you had an experimental animal who was available. And in those days they cost $25 so we had quite a few monkeys.

And under Enders' leadership we worked with the virus first in primary human kidney cells, then in primary human amniotic cells and then Enders said, “Well you know if we are going to have a vaccine virus we've got to get out of human cells. Maybe if we get into some other species we'll pick a virus attenuated.”

And indeed we went to embryonated hens’ eggs and passed the virus a number of times.

And then in chick embryo fibroblasts. And that material from the chick embryo fibroblasts produced a cytopathic effect, which we could observe. And that became the material then that we tried to compare and contrast to the original human kidney virus. And indeed when we put the chick virus into monkeys they didn't develop viremia, they didn't develop fever, they didn't develop any sort of nasal congestion or conjunctivitis or rash, they were perfectly fine. But they developed antibodies. And when we later challenged them with the early kidney virus they proved totally immune. So we were on our way.

So you had your attenuated virus now. How did you decide to take the first step to administer it to a human being?

Well there was an institution outside of Boston in Waltham called the Fernald School in which youngsters were housed with various neurological and central nervous system problems. And they used to have outbreaks of measles every two or three years with significant morbidity and indeed some mortality. So we went and talked to the director and we talked with about 20 parents of children who'd never had measles. And they agreed that they would have their children participate in these studies. So we injected these youngsters with the chick cell virus and observed them daily. We did throat cultures. We did blood cultures. And they never had any viremia, they never had any virus in their throat. At the end of several weeks they had antibodies to measles virus. So we had made the big jump. Several years later they had another big outbreak. They didn't get disease, when all the other youngsters did.

That really is remarkable. Did you have a sense when you saw these results of the implications of your findings for childhood health both in the United States and globally?

I must say I was fairly parochial and I had very little idea of the global impact of measles. I certainly knew what it was in the United States. And we mobilized a group of colleagues who were clinical
investigators in New Haven at Yale, in Boston at the Children’s Hospital, in Baltimore at Hopkins, in Denver at the University of Colorado, in Cleveland at Case Western Reserve, in New York at Bellevue. They were all very anxious to go ahead and study this. And they went ahead and used the vaccine in home-dwelling children rather than in institutional children. And they were very pleased with the results. The publication of these results then resulted in a large number of individuals going ahead and getting vaccine virus to immunize children. And within a few years, actually by March of 1963 – it was just the 50th anniversary last March – the government licensed the vaccine and it became available.

And I think this is an interesting point regarding your question about John Enders. You know the Polio vaccines were Salk or Sabin, named after the investigators. The Measles vaccine was not Enders it was Edmonston because that was the name of the boy from whom the virus was originally isolated. And over the years derivatives of that virus have been used throughout the world as measles vaccine. I thought that was very reflective of the kind of modesty that John Enders had as part of his personality.

And it sounds like he also elicited that sort of modesty in his mentees. Because it seems to me from my reading that you played a very major role in the development of this vaccine because you were the only physician on the research team.

That is true. People turn to me now and I guess it’s because I’m the only survivor. There were three of us really who were essentially involved from the beginning right up until the end. And one of course was Enders, the other was a fellow from Yugoslavia named Milan Milovanovich. And I was the third but as you say I was the clinician so when we got involved with human studies obviously I was the leader.

You had alluded before to what you described as your parochial perspective about Measles. What happened subsequently to change that?

That’s a very good question. It opens a whole other chapter in my life. The original studies were published in 1961 in the New England Journal and people began to read these and we began to get inquiries from all over. But the fellow named David Morely who was an English pediatrician working in Nigeria, kept email -- not emailing we didn’t have email then -- he kept telegraphing us and calling us and saying “You have to come to Nigeria and use this vaccine,” and “We have a mortality rate of anywhere from five to 15 percent of children who get measles in Nigeria die of measles.”

Well Enders was very thoughtful and conservative and said, “We’re not going to take vaccine to Nigeria until it’s been proven that it’s safe in American children, otherwise we’ll be accused of going to use these poor Nigerian kids as guinea pigs.”

Well by the time we had all of these studies completed that showed the safety of the vaccine in the U.S., there were six or seven pharmaceutical firms which were producing off-shoots of the Edmonston vaccine and Merck was one of them. And with assistance from Merck, Maurice Hilleman was their leader of their group, I took vaccine and went to Nigeria where I worked with David Morely. And the mothers were desirous of having vaccine for their kids. One of the common statements was you don’t count your children until the measles has passed, because they were used to losing children with measles. So we went ahead and studied children at a little village called Imesi outside of Ilesa, and fortunately the vaccine worked very well in these children. They didn’t have any trouble with it and they developed immunity.
And what we learned – and this was very much from David Morely – that it wasn’t that the virus was any different in Africa, it was that the children were different. They had malaria. They had protein depletion. They had vitamin A deficiency. They had intestinal worms, so that they were pushovers for a virus like measles and that was the cause of their morbidity and mortality, not that they were getting a more virulent virus, they were getting the same virus you got in New York or Boston but they were very different hosts.

The other thing was they got very sore mouths. These children were mostly breastfed. And they would get diarrhea with measles. They would stop breastfeeding because their mouths hurt, so they would get marked dehydration in addition to all these other things we’ve mentioned.

**Very interesting and a good example of how an intervention globally can be so remarkably effective. I want to now shift from that to really that sort of ironic counter-balance to this progress, which is - how do you view this whole anti-vaccine movement?**

Well Andrew Wakefield wrote a paper in *The Lancet* in which he claimed that the MMR vaccine – measles, mumps, rubella – caused autism and that it was the measles component. Well, eventually it was proven that this was totally false, that he had invented much of the data, that the laboratory work had been inappropriate, and eventually he lost his license in England and ended up in Austin, Texas. But he was considered a martyr by the people you are talking about. There are some people, they are just anti-vaccine. On the other hand, I think the greater majority of those who don’t want their children vaccinated are what I call vaccine-hesitant, because they are uncertain. And you know measles in the 21st century is a disease most of these people have never seen. In fact many of the health personnel – physicians and nurses – haven’t seen measles because it’s been eliminated from the United States since the late 1990s.

**You have a very generous attitude to a group that is very challenging for us to deal with. And I know this both as an ID specialist myself and also as a doctor who is married to a pediatrician.**

I think that the problem of vaccine hesitancy is such that when we get quote “outbreaks of measles” they are almost always among unvaccinated children.

It’s not just measles. It’s the idea that kids are getting measles vaccine, they’re getting whooping cough vaccine, they’re getting rotavirus vaccine… On and on and people look at the multiplicity of vaccines and think, “God, this is going to overwhelm my child’s immune system.” Well it’s been shown very well that the number of antigens put together in all the vaccines doesn’t even equal what children used to get years ago in the original pertussis vaccine. I think it’s just one of those things - a mixture of the past and the present and confusing them all.

**Sam this has really been a fascinating discussion. I wanted to just ask you, if you had anything, any last comments to make before we stop?**

I would make one comment, which is one of the things that’s probably been most helpful in keeping diseases such as measles and rubella and hepatitis at very low levels in this country has been the fact that we have school entry requirements. That is in most states a child can’t go to school unless he’s fulfilled the recommended immunization schedule. Now there’s so much noise about this but the total percentage nationally of children for example getting measles vaccine is well over 90% and that’s
sufficient to keep us from having big outbreaks. Right now, for example there’s an outbreak in California. In all these instances the virus has been proven to be imported – from Japan, from the Philippines, from France, from Italy. Measles is the most highly transmissible virus. So that it finds those susceptible.

This is one of the unique features of what’s happening today with measles in this country. As I say if we have 150 or 200 cases we think, “My god that’s an outbreak.” On the other hand, if you look at what’s going on in the European countries, you know, the Netherlands is having 2,400 cases of measles a year. Germany 1,700. Italy 2,200. Turkey 7,400. When you compare our having just a couple of hundred cases to those countries, which are just as affluent and just as knowledgeable as we, having thousands of cases. They don’t have school entry requirements.

Exactly that gives me new appreciation for them. Ok thank you very much Dr. Katz and once again this is Dr. Paul Sax, Editor in Chief of Open Forum: Infectious Diseases, and we’ve been speaking with Dr. Samuel Katz, the pioneering vaccine researcher and we’ve been discussing in particular the development of the measles vaccine. Thanks so much for listening.