

FOCUS: VACCINES

Pediatric Infectious Disease Epidemiology: Prevention Trumps Treatment

An Interview with Marietta Vázquez, MD

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Marietta Vázquez, MD, is an Associate Professor of Pediatrics and of Nursing at Yale School of Medicine. Dr. Vázquez received her BA from Yale University before obtaining her MD from the University of Puerto Rico in 1994. After completing her MD, she returned to Yale for a residency in Pediatrics and a subsequent fellowship in Pediatric Infectious Disease.

Dr. Vázquez began as an Associate Research Scientist at Yale School of Medicine, where she worked closely with Dr. Eugene Shapiro, pioneer of the Investigative Medicine Program at Yale. Together, they demonstrated the effectiveness of the pediatric varicella vaccine, approved for use in the United States in 1995, and determined that two doses of the vaccine significantly reduces the chance of contracting varicella when compared with a single dose. In addition to varicella, Dr. Vázquez has also made substantial contributions in understanding the effectiveness of the pneumococcal vaccine. Most recently, her work has focused on understanding viral protection in newborn children through maternal immunization.

In this interview, Dr. Vázquez discusses her initial interest in pediatric vaccine epidemiology and how it has developed throughout her career. She addresses the current status of the vaccine field both from a scientific as well as a socioeconomic standpoint. Finally, she comments on the future of vaccine research and infectious disease with specific emphasis on maternal immunization as a novel avenue for viral immune protection among infants.

You've had a unique opportunity to work with a lot of different groups of people. Some of your earlier work focused on the varicella vaccine and its effectiveness in preventing chicken pox, which really helped shaped the landscape for the dosing of that vaccine. We were wondering if you could tell us a little bit about your background and how you got excited about vaccines.

I got interested in vaccines through what got me interested in pediatrics. When I decided I wanted to be a doctor and had to decide on a subspecialty, what interested

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me about pediatrics was the idea of rather than only treating diseases, [we try] to prevent them. I think that is at the base or the root of pediatrics, that really what we do is we try to prevent [disease]. It is sort of a nature of our patients because [of] the time we reach them — they are not adults, they are children, who are still growing and developing. Also, in terms of research experience, my first few experiences with scholarly activity were at the Centers for Disease Control as a medical student, and I got to see the clinical epi[demiologic] side and really look at how clinical research studies could have a direct impact on the health and management of populations. If you put those two together, a type of work where you are dealing with large populations and where your results have a direct and clear immediate clinical impact on prevention, if you merge those two, you mix them in a pot, you come up with a vaccine. And on top of that, I was fascinated by infectious diseases.

I am originally from San Juan, Puerto Rico, and my family are Cuban immigrants. I did my undergraduate [degree] at Yale and then went back home for medical school. This was the early 1990s, and it was the peak of the AIDS epidemic. In Puerto Rico, the AIDS epidemic was an epidemic of children, whereas here in the United States, it was mostly [an epidemic in adult] males. But for us [in Puerto Rico], it was very much the families, and it probably had a lot to do with intravenous drug use. I was a medical student. I was already interested in pediatrics, and I had all these children who were dying from AIDS, and we didn't know what to do. I knew that I wanted to do infectious diseases, and I had a background and interest in clinical epi[demiology] and prevention, so if you mix all of those, it was a natural progression. The specifics, in terms of [an interest in] vaccines, came [from] two things: one, as a resident in clinical practice, I got to see the impact that the vaccines had on my patients; the other was mentorship, which is one of the most important aspects for people training in their careers — to really connect with a mentor. My mentor, Eugene Shapiro, had a long and very prolific

and well-known career in vaccines, so when I started working with him, it seemed like a natural progression to work on vaccines. I came here in 1994, so this year it's been 20 years. I've spent 20 years looking forward: "What am I going to do and where am I going to be?" This year has been a year of a lot of reflection: "Why am I where I am and where do I want to go next?" A lot of people call me Dr. V, and they say that V is for vaccines, not for Vázquez.

The chicken pox study was the longest clinical study of varicella. When I look back, I see it as one of my children because I learned a lot of what I know about vaccines through that study. It went on for close to 15 years. It was very much a learning curve for me in terms of learning about the virus, learning about the vaccine, learning about and being able to conduct a study, and seeing how this infection went. If I were to give an example of the power that a vaccine has, there is nothing more powerful than watching, being part of that progression where you see a disease like varicella that was the bread and butter of pediatrics — everybody had chicken pox and nobody thought to call a medical student or a trainee to say "come look at this case of chicken pox," because it's like calling somebody and saying "oh, I have a cold, come look at me" — and how that went from bread and butter pediatrics to a fascinoma. We don't see chicken pox anymore. Through this study, I learned about methodology, clinical epidemiology, and study design and how to adapt the study to answer all of the questions from "does the vaccine work in everyday practice" to "how long will the vaccine work" and "let's look at long-term effectiveness and then look at what is the ideal age to give this vaccine; is it 12 months, is it 15 months, is it 18 months?" Within the lifespan of the study, I was able to not only learn all of these different techniques and be able to change the study or the methodology to try to target the questions that we didn't anticipate in the beginning, but also see what was going on in terms of the epidemiology and watch how the number of cases dropped. And now, in 2014, if there is a case of chicken pox, I call

every single person to come in because it [has] turned into a fascinoma; nobody sees chicken pox. That transition, in and of itself, to me as a vaccinologist is one of the most exciting things; it is the power that a little vial has, not only to impact the health of one child, but the health of populations. That's what I learned through that study, and I was able to apply [this knowledge] to other studies such as the pneumococcal study, which earned us the Charles C. Shepard Science Award. When the pneumococcal vaccine came on the market, I was ready. I had learned; I knew the methodology; I knew how to [study] it, [along with] Lyme vaccine, influenza vaccine, others. So if you were to ask me what excites me the most or what I think is one of the things that keeps me in the field of vaccines, it is the power that vaccines have and their impact on populations.

More recently, you completed a study on the flu vaccine in pregnant women and how it affects infants and their immunity. Could you tell us a bit about this work? And where are you going from there, what is your next project, and what are you most excited about?

I will start out by telling you that the highlight of my career is actually right behind you [points to a photo of her daughter accepting an award from the President of the Infectious Disease Society of America]. This study [Benowitz I, et al. Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. *Clin Infect Dis*. 2010;51(12):1355-61], which I will tell you about in a second, got a big award. Unfortunately, it was going to be given on a day when I was out of the country speaking about vaccines. My daughter, who was 9 at the time, heard me talk about how sad I was that I couldn't go to accept this award. She said, "Mama, I have the solution. We have the same name." Her name is Marietta also. She said, "Why don't I go and get the award?" I thought, "You're crazy." This was not even a pediatric meeting; it was an adult meeting, but she kept telling me that

she was going to go get this award. The event was in Boston, and I contacted the people who put it together, the Infectious Disease Society of America. I think they were tickled pink; they said, "Have her come." In a plenary session, with a couple thousand people, when they announced it, she got up and shook the hand of the President of the Infectious Disease Society of America. He tells the story of how he sees this little girl, and he thought he would shake her hand, and she would not speak, but she grabbed [the award], went right to the podium, pulled down the mic and thanked everybody, including — this is awesome — my collaborators. I thought, "*Adults* forget about thanking the collaborators." Anyway, that's the highlight of my career.

Influenza is a very common disease, and one of the things that frustrated me was that this very common infection for which we had a vaccine, we couldn't give to children under 6 months of age. The vaccine does not work well in infants. So we thought, "What are different ways to protect the infants?" We know that pregnant mothers in the last trimester pass antibodies to their infants, and we thought, "Could we test that hypothesis?" It's looking at protection in a different way. Rather than immunizing an individual so that individual can develop the immunity, [we] would be able to immunize the mother and have the infant be immunized in an indirect way. The study was actually championed by Isaac Benowitz, who was a medical student here at Yale working on his thesis with me. We did a study that took us 3 years to conduct. It was very labor intensive. We enrolled children under a year of age who were hospitalized with influenza, then we enrolled children who were in the hospital at the same time who were the same age as the kids with influenza [as a control group], and then we looked backward in time to see how many of their mothers got the [influenza] vaccine. Through that study, we found that infants who had mothers who were immunized during pregnancy were 94 percent less likely to be admitted for influenza. It was the first time that it was shown in the United States that giving a mother the influenza vaccine

during pregnancy protected the infant. The results were beautiful because we purposely included children up to a year of age. Children at 6 months of age could get the vaccine themselves, but there were many who didn't. So we were actually able to look at the protection in the first 6 months of life, which is more or less the half-life of these antibodies. We knew that the antibodies you get from your mom by 6 months of age were probably all gone, and we were able to assess the effectiveness of the vaccine in those first 6 months of life and in the following 6 months. It didn't work 6 months to 12 months of age, which goes hand in hand with what we thought would happen biologically.

So [after the study] we said, "Well, then what?" As a clinical epidemiologist, it was very much a learning experience for me because here I had these great data, they need to be put into practice, but there were more steps. At the time, fewer than 20 percent of pregnant women were receiving the influenza vaccine. I realized that I could have great data, but if these data in a journal don't really relate to what happens in every day practice, there were gaps.

We came up with an idea to study barriers and facilitators. A PhD nursing student from the University of Connecticut, Pamela Meharry, and I did a qualitative study. This was brand new to me — I am a clinical epidemiologist, quantitative, not qualitative. We did focus groups with pregnant women and women postpartum in Greenwich Hospital, where Pam Meharry worked, and also in Bridgeport, two very different populations, and asked the moms, "Why did you get [the] influenza vaccine or why didn't you?" We went back to the drawing board to learn from the patients. In that study, we identified barriers and facilitators toward influenza vaccination. We learned something very important, and it was education. The reason why many of the mothers who didn't get the vaccine was because their obstetricians didn't offer it, but some of them didn't know that if they got the vaccines themselves, they could protect their babies. We said, "Aha!" We needed to get our message out, not only to the doctors, but also to the moms, because

the moms told us, "Had I known it was good for my baby, I would've said yes." So we put together this beautiful educational brochure in English and Spanish with basically the take-home message of "two for one." Get one shot of the vaccine, it's cost effective, and you and your baby are going to be protected. Then one of my colleagues in clinic said, "How do you know it works?" That led us to do another study where we did a randomized clinical trial in which some of the moms got the educational brochure and some didn't, to see if it changed practice. In that study, which we published last year, we found out that indeed it made a difference.

So that was the progression of going from the vaccine science that I was very comfortable with and realizing that your results are only as good as the impact that they have and just developing good data is not enough. That has led to all sorts of educational interventions at the national level. The Academy of Obstetrics and Gynecology now has a task force focused on educating their providers and the lay press. By no means am I leading you to believe that it is all due to our projects, but I think we had a small piece in raising the awareness on both sides.

That leads into our next question. Here in New Haven, CT, we have quite a diverse population with varying degrees of hesitation surrounding vaccination. What struggles do you face in educating others about the importance of vaccination, especially when there are all kinds of cultural, religious, and socioeconomic barriers that have to be considered in patient care? How do we overcome these aspects and better educate the public?

I'll answer that from my personal and clinical perspective, and then I'll answer that more from an overall public health point of view. It is very challenging, and by no means do I have the answer. It is a very complicated and multifaceted problem with tons of layers. How do I approach it? I work with residents directly. Yale has a Pediatric [Medicine] training program, and I am one of the Associate Directors of the residency pro-

gram. Not only do we have to develop our way to approach the patient, but it is also one of my jobs to help trainees feel comfortable and to train them on how to address this problem. We are fortunate that in this area of the United States, our problem with the anti-vaccine movement is not as large as in other areas of the country, but it is still [enough of] an issue that yesterday when I was in clinic, I had to address it.

We are very good at giving advice, at talking, but I think that one of the hardest things for me to learn was to listen, to really listen to the patients. The only way you can successfully address a question is by listening to the question and really understanding where they are coming from. So when somebody says, "I don't want the vaccines," I will say, "Tell me about it," "What are your concerns, what have you heard?," "Do you know of somebody who had an adverse event in vaccines?" You start by listening and by asking questions, turning it around. Sometimes it is not somebody who is anti-vaccine, [but] it might be somebody who read something on the Internet. Maybe it was TV, maybe it was the Internet, or maybe it is a family member with autism. Maybe it is a parent of a child with febrile seizures and the child had a vaccine that gave the child a fever, and if they are predisposed to a febrile seizures, [the vaccine might have induced a seizure]. So listening is the first very important step.

The next one is not to indoctrinate. We are all independent human beings; parents have the ability and the right to make decisions. Do not preach; do not indoctrinate. We just give information, and I'll be very frank with parents. I will say, "Ultimately, it is your decision, but this is my area of expertise; let me tell you about this vaccine." I talk about what the vaccines are, what is in the vaccine, what is not in the vaccine, because there are a lot of misconceptions in terms of the things that are inside vaccines. Some people still think that there is mercury. If I realize that [mercury] is one of their concerns, then I get very specific about the amount, that there is no mercury. I compare it to when there was mercury, talk about the type of mercury and

compare it to the mercury that you find in a tuna fish can, for example. I will be very specific and give information. I also make sure that I talk about the diseases in question, because oftentimes parents will say no to the measles, mumps, and rubella vaccine, but I feel that it is my job as a physician to remind them that there are current outbreaks of measles in this country and to talk about what nobody wants to talk about: that children can die from this. We can give them literature and time to decide.

Am I successful in giving the vaccine? Not always, because I think in the end my goal is not to make them think like I think; my goal is to help them make an informed decision and then even if they still decline the vaccination, I've done my job. Oftentimes what happens is some doctors will say if you are against vaccines, you can't come to my practice. But my view on that is then they will turn around and go somewhere else until they find somebody who is okay with having them at their practice. It is a very important problem; it is a problem that continues to grow in the United States, and it is starting to percolate into other countries. I do vaccine work in other parts of the world, and I have the privilege of visiting other countries and can see over the years how, with the Internet mostly, more and more people are starting to question [vaccines].

We want to get your perspective on where the future of this field is going. How do you see vaccines progressing both from a science/medical standpoint, but also from an epidemiologic/public health standpoint? Although we have many vaccines for fatal infectious diseases, there are many diseases that still lack treatment or prevention. What do you think are going to be the hurdles as far as getting people to do the research as well as to choose to immunize against the infectious diseases that may or may not be quite as life threatening as something like HIV?

I think it is an extremely exciting time to be working on vaccines, because if you

look at the pipeline, if you compare the number of vaccines a child received 20 years ago to now, there really [has been] an explosion in the number of vaccines that children are receiving. And if you look at the number of vaccines that are coming down, it is very fascinating. Very soon we will have vaccines against Dengue fever, which may not make such a large impact in the mainland United States, but definitely will in other countries. I think it is a great time to be in vaccines from a science point of view. The other thing that I am very excited and hopeful about is the fact that there is a global view and movement toward vaccinations. Years ago, the new vaccines were given to developed countries, very wealthy countries, but [now], entities like the World Health Organization, Gavi the Global Vaccine Alliance, the Bill and Melinda Gates Foundation, and The Clinton Foundation [are changing this reality]. All of these entities, not countries, but private entities have really changed the view [on vaccination], made it a more global issue.

The rotavirus vaccine, a vaccine that I am currently researching and have been very much a part of the vaccination program both in the United States and internationally, is a beautiful example of a vaccine that is very expensive, that was developed and licensed in the United States, and almost concomitantly was available in developing countries because others made manufacturers pledge that part of the development would be that it would be made available to developing countries at a lower cost. I think that is both very inspiring and very exciting and makes vaccine work all the richer. Now we can say we are rolling out a rotovirus vaccination program in the United States, and at the same time we don't have to wait 10 years for the patents and licenses to go down to make it affordable, so you can actually study them in both places at the same time and address some of the challenges.

I think it is a very exciting time. The challenges of vaccines are that they are very expensive, they're very labor intensive, and it takes years for these very large clinical trials to go through. Although I think it is great

that many vaccines are coming to the market, the speed at which these vaccines are coming and are available to us is not fast enough. There is also the challenge of how many vaccines we can give. We'll really have to sit down and make decisions [when we reach] a point where we [may have too] many vaccines. The future of vaccines is globalization, adult vaccination, vaccination for the elderly, and immunization in pregnant women. The latter really excites me, both because of some of the work that I've done in immunization of pregnant women, also referred to as maternal immunization, and because I think that is very much where the future of vaccines is headed in terms of preventing disease in early infancy. But it is very challenging; it is changing the landscape. Nobody wants to touch pregnant women because of the legal aspects of it, but I think that is fascinating. I can tell you that there are many other vaccines [on the horizon] such as Dengue vaccine, hopefully even a malaria vaccine, a group b strep vaccine for the infants, and a staphylococcus aureus vaccine, a bacterium that is quite common.

The other thing that has been really instrumental and probably one of the most exciting parts of my career so far has been to be part of the Advisory Committee on Immunization Practices. This is what I call, for a vaccinologist, the Disney World of vaccines. Three years ago, I was asked to be on this panel. It is [comprised of] 15 experts around the United States, and we create policy for vaccination in this country. It has been fascinating from a learning point of view because I had a lot of experience in the research aspect and in some public health, but this really opened my eyes toward how vaccine policy works. Now I am part of this group that is responsible for voting whether to put a vaccine on the schedule for the rest of the United States. It has really been humbling and a very important learning experience for me and given me a more global view of how intricate vaccine decisions are, both in the United States and internationally. [I'm learning that] it is not only vaccine development and finding data through your studies

whether a vaccine works or it doesn't, [but also] that when the nation makes decisions on whether to include a vaccine or not, we need to take into account the impact it is going to have on entire populations: "Can we afford it, can we not afford it, where is it

going to be in the overall schedule, how do we move forward with vaccination programs for adults, for adolescents, for pregnant women?" Overall, I think it is a very exciting time, and you have your finger on the pulse for having an issue on vaccines.