Female: Welcome to Conversations on Health Care with Mark Masselli and Margaret Flinter. A show where we speak to the top thought leaders in health innovation, health policy, care delivery and the great minds who are shaping the health care of the future.

This week Mark and Margaret speak with Dr. Ofer Levy, Director of the Precision Vaccine Program at Boston Children's Hospital, and member of the FDA COVID vaccine advisory panel on the pending decision on vaccines for younger children and a recent decision to recommend boosters for older Americans. He discusses the emerging era, precision science that has been spurred on by the pandemic.

Lori Robertson also checks in, Managing Editor of FactCheck.org looks at misstatements spoken about health policy in the public domain, separating the fake from the facts. We end with a bright idea that's improving health and wellbeing in everyday lives. If you have comments, please email us at chcradio@chc1.com or find us on Facebook, Twitter, or wherever you listen to podcast. Now, stay tuned for our interview with Dr. Ofer Levy here on Conversations on Health Care.

Mark Masselli: We're speaking today with Dr. Ofer Levy, Director of the Precision Vaccine Program and Director of Infectious Diseases at Boston Children's Hospital. He's Professor of Pediatrics at Harvard Medical School and is an associate member of the Broad Institute of MIT and Harvard.

Margaret Flinter: Dr. Levy is a member of the FDA's COVID vaccine advisory panel, which just issued recommendations for vaccine booster shots for certain populations. His team is one of many that's worked on versions of the COVID-19 vaccine. Dr. Levy, welcome to Conversations on Health Care.

Dr. Ofer Levy: A pleasure to be here, Margaret thank you.

Mark Masselli: And Dr. Levy, you serve on the FDA COVID Vaccine Advisory Panel, which has been in the news. Your expertise is in that pediatric immune responses and precision vaccine development. It was looking like that the 5 to 11 year olds were back on track to be approved for emergency use authorization of the Pfizer vaccine by Halloween. But some say now it may not be until Thanksgiving. Maybe tell our listeners what the timeline looks like to you on the vaccine authorization for younger children.

Dr. Ofer Levy: Thank you for that, Mark. This is a very important question. We face an unprecedented pandemic. We're very fortunate that the mRNA and other technologies had matured to the point that they were ready to be deployed against this threat. We're fortunate that we have safe and effective vaccines. Yet, individuals vary in their immune

response, in their physiology, and we cannot assume that data in one age group applies exactly the same way to another age group. In fact, we've seen those differences just in terms of how the infection is operating. It's hitting the elderly particularly hard, older adults with higher rates of mortality, etc.

When we convened as an advisory committee recently, we were asked an initial question by FDA of whether we would recommend a booster or third dose of the Pfizer mRNA products for individuals 16 years of age and up. That first question got voted down by a pretty large margin. I was one of the votes against. The reason was that, most of I can't speak for the other members, but from the conversation what emerged was, most of us felt there was not enough safety information for the booster dose, particularly in the younger age groups. Then after some discussion, we rephrase the question for 65 years and up and those at risk of severe COVID, and that overwhelmingly passed, I think it was by consensus, a 100% vote.

Then we believe we might get there for younger age groups. But we need to see the data, and the sponsor, I believe will be back in this case Pfizer with more data in younger age groups for safety and efficacy. Then we're going to call it as we see it, I can't prejudge any data I haven't seen yet. I do think it's important for the studies to be done.

Margaret Flinter: Well, Dr. Levy, you've made the point that all of us as parents and health care people know that children are not just little adults, right? You certainly want to make sure that we have the protocols for testing and determining safety and efficacy of these vaccines for younger children. But for our audience, maybe just talk a little bit besides settling out what's the proper dose. What are the added risk factors unique to younger children and vaccines the, additional worries or concerns. What kind of reinsurances are we looking to be able to offer to parents that vaccines will one be effective, but most of all, that they'll be safe?

Dr. Ofer Levy: Well, I think the message to parents and to all Americans is that we have to let the process take its course. We have a good process In the United States through the Food and Drug Administration or FDA, the sponsors whether they are Pfizer, Moderna, J&J or other companies that have Coronavirus vaccines submit data to the FDA. Pfizer has announced that they have generated data in children 5 to 11 years of age. They believe those data indicate safety and efficacy in that age group. That's welcome news. But we need to take an independent stance, we have to see those data and review them. Vaccines you give to healthy people, so they've got to be safe, safety comes first. We don't presume because it's safe in one age group that it's safe in another. We're going to take a very careful eye to the data, we have

to let the process take its course.

It's a good process. It's a public deliberation, the members of the committee are not allowed to meet in closed session. We're not even allowed to email each other about the topic. Everything we transact, any information we discuss is in public and on the record, and there's public commentary phase as well, for any American of any point of view, to express themselves, so we believe that's a good process. I look forward to a very open and frank conversation with FDA and with the sponsor, and we will have to come to the best decision based on the information available.

Even when a vaccine is authorized or approved, we continue to keep an eye on safety. We have surveillance systems, the FDA, the Centers for Disease Control, or CDC have safety surveillance. Some of you may know the V-Safe app, when you got [inaudible 00:06:32] you could opt in on your iPhone, and you answer surveys about say so if any signals are detected, we have seen entire programs shut down making the news right with a J&J has presented, shut down even with very rare cases. I believe the public should look at all of that and say the system is working. We're taking safety very seriously.

Mark Masselli: I want to pull the thread on the process and the system, wondering if at some point there'll be a retrospective look at what do we do in a global pandemic. I think you're absolutely right. The very staid process the FDA has been a great one, served us well in our country. But as you think about lethality and transmissibility being much greater, do you think that there is a different process that the FDA might consider as it looks out into the future, because we certainly have to prep for these types of global pandemics to continue. What's your sense about that retrospective analysis that what's your own view on it?

Dr. Ofer Levy: Well, that's a complex question. I mean, you know, we want to be rigorous, and we want to put safety first, and we want a system that can respond efficiently to challenging circumstances like a pandemic, that's the whole basis of the authorization, right. The authorization is short of a full approval, and moved forward pretty rapidly. If that was a standard approval process, that would have taken a lot longer, so we went with about two to three months of follow up data for the safety, reasoning at that point that the pandemic was killing a lot of people, and that to the extent that vaccines have side effects, they're reported in the first days and weeks after a shot. There are no medically proven side effects that mysteriously arise many months later, or years later, after a vaccine just in general looking at all vaccines. That was the basis for deciding on two to three months of follow up safety data.

Beyond that, once the sponsor submits the data to FDA, FDA understandably need some time to look at it. These are complex

datasets, they have to be looked at statistically, and then that has to be packaged for the advisory committee, etc. Are there steps there that could be even faster? I don't know, maybe. But we've got to keep safety first, so we've got to keep the integrity of the process. If we push it too hard, then we have cutting corners, and that that would not be wise in my mind because the public wants to know we're taking the safety very seriously. If we make a mistake, that can have very negative consequences, not just during the current pandemic, but just in the general confidence in the vaccine enterprise. The calculus around this is delicate, and I think the system has done a pretty good job under the circumstances.

Margaret Flinter: Well, I agree. I have to say I can't think of a single day since March of 2020. When COVID vaccine, COVID testing wasn't on the front page of the newspaper, so the whole country has had kind of an education in how this whole pandemic has unfolded and our strategies to control it. Certainly when the FDA Vaccine Advisory Panel issued a ruling on COVID vaccine boosters for the general public and recommending boosters for people 65 and over and those with underlying health conditions. They rejected a booster for the general population, recommend it for people 65 and over and those with underlying health conditions, but the CDC, which also overrode some of the recommendations and expanded the categories of those to be eligible for a booster shot. Tell us more about the science that led to that decision. Also, from your point of view, the likelihood we'll see a change to those recommendations as more data comes in?

Dr. Ofer Levy: Well, you know, we are still learning how these vaccines are protecting occurrence COVID, they do. They protect best as against hospitalization and mortality, even against the Delta variant and other variants so that's the good news. That's why everybody should get immunized. Vaccines vary in their durability, how long does that immune response last in a way that's protected? We're still learning as a global biomedical community, the duration of protection after these vaccines. But there's some data to suggest that there's some waning of immunity, and that's to be expected to some extent.

The antibodies diminish over time, we think the antibodies are important for protection. There may also be T cell immunity, cellular immunity against the virus, so we're still defining all of that. But there's some evidence that they come down not unexpectedly, the antibodies with time. There was some evidence from the data in the US and in Israel, that with increasing time since immunization, you have an increased risk of infection. Now, that's complicated to sort out, because at the same time the variants change. Was it due to the antibody coming down, or was it due to the new delta or some combination? That's a little hard to tease apart. But the bottom line is, there was the impression, particularly in those who are older people

with weak immune systems, that a booster benefit would outweigh any risks known for the booster.

As you get into younger and younger age groups, the risk of severe outcomes drops and the amount of safety data around a booster is less, so therefore the risk benefit now didn't seem as compelling. But we are agnostic for the future. In other words, there was likely going to be more data collected, and sponsors whether it's Pfizer, Moderna, J&J will be bringing those data to FDA and FDA will determine when it's time for us to sit and look and say, hey, maybe it's time to go down now, to lower age groups. That's perfectly possible, certainly what the state of Israel has done.

Mark Masselli: We're speaking today with Dr. Ofer Levy, Director of the Precision Vaccine Program, Director of Infectious Disease at Boston Children's Hospital. He serves on the FDA COVID Vaccine Advisory Panel. Dr. Levy, when the pandemic struck, there were already other vaccine studies underway based on the mRNA technology and your own team began working upon this much earlier, working with Dr. Peter Hotez, who we've had on our show who developed a vaccine to address the SARS outbreak and which I think really set the stage for developing a COVID vaccine far more quickly. I wonder if you could just talk about that trajectory and why it matters when talking about how swiftly these vaccines were created, because it was over a longer period of time, at least the platform that was used.

Dr. Ofer Levy: Correct. A lot of these are technologies that have matured over the years. You highlight the leadership from Dr. Peter Hotez and Maria Bottazzi and the group at Baylor, they had worked on the earlier version of SARS. Then of course, as that epidemic dissipated, there was less interest in funding in moving that work forward. But their work was seminal years ago and allowed us to get out of the gate. They provided us very valuable spike protein antigen to work on. Our group here at Boston Children's Hospital, I direct the Precision Vaccines Program. We're bringing precision medicine principles to vaccinology. How do we understand the immune system varying with age? How do we build vaccines that are tailored to a particular susceptible population? Right off the bat, we started to collaborate with Keater [PH]and others to develop a vaccine that would not require freezing that was highly active in the elderly.

Our group has strengthened adjuvants. Adjuvants are molecules that boosted immune response. These are like rocket fuel for the immune system. These molecules you can add to a vaccine to get the vaccine to work better, possibly even a single shot protection, high levels of antibody. It turns out that different age groups respond differently to these immune enhancing molecules, these adjuvants. We modeled human elderly responses outside the body. We had members of my

synagogue in Cambridge come in and donate blood, older individuals 60, 70, 80 years old at the height of the pandemic coming in bravely and donating blood so we could test it outside the body and find the best adjuvant for that age group, and then test it in elderly mice and showed that this vaccine that we created was at least as effective as the Pfizer vaccine.

Now a company is advancing a similar concept with these same adjuvants in India. I think the company's called Biological E and they work with Peter Hotez and their group. It's been a very powerful collaboration. We recently released our data, and it's under review at a nice journal. We're very proud of our team's work, and we thank all of our collaborators around that. This pandemic really, in many ways brought out the best in people working together across academia, industry and government to accelerate vaccine development, and we need those vaccines because right now, across the globe, there's a shortage of vaccines. In Africa, for example, only 1 to 2% of the population has been immunized. It's a moral outrage. There's a lot of work to be done. How can we develop vaccines that give single shot protection that are safe and effective, easy to transport, and this is really a challenge.

Margaret Flinter: Certainly one of the great frustrations in the midst of this has been addressing the issue of vaccine hesitancy or vaccine flat out resistance, despite all the evidence of how well vaccines work. We have decades of history and hundreds and thousands, millions of lives across the globe that have been saved. But just recently, it seems we're making some progress, perhaps with previously resistant populations.

I wonder what your thoughts are, it seems part of it, as we read about in New York City, where municipal employers or businesses are mandating it, that may be one thing that's pushing people to get the vaccine. But I'm also reading that it's really the Delta Variant that people have heard enough now about how dangerous it is, really to all ages, that that may finally be the knowledge that is overcoming some of this resistance. What are you seeing in the data around the country or just what you're hearing from the people that you're working with about overcoming this hesitancy and resistance?

Dr. Ofer Levy: When we convene as an vaccine Advisory Committee, there's a public commentary phase. Together with a colleague of mine, Elisa Weitzman we systematically analyzed all the public commentary around the mRNA, vaccines Pfizer and Moderna. As you might imagine, we have Americans of all points of view weighing in, pro-vax, anti-vax, in between vaccine hesitant, and that was very instructive. We published that work recently. Now we're looking at the commentary around the booster dose meeting. As Americans learn

more and more about the virus and the vaccines, attitudes evolve. More people are coming forward to endorse immunization. I know that in a range of communities uptake has increased, including in the African-American community, we welcome that news. Yet still, there are people for a range of reasons who are vaccine hesitant or resistant.

In some cases, information helps. In other cases, people have made up their mind and they have a certain stance and a certain belief. You know, we have a large heterogeneous country with a lot of different points of view. But we have to continue this respectful communication. The vaccines are, yes for ourselves, our loved ones, but for our entire community, for getting our economy back on its feet, getting the schools reopened and getting back to some semblance of normality here.

Mark Masselli: Dr. Levy, we were recently talking about the silver lining of this pandemic experience with your Harvard colleague, Dr. Michael Mina. We really talked about the acceleration of scientific discovery spurred by the urgency of the pandemic. The idea that we can vaccinate against emerging infectious pathogens is, is one thing, but the idea that vaccines could prevent cancer or HIV, even opioid addiction seems like futuristic fantasy. But actually, there are people like yourself who are working hard on many of these, you're doing it at the Precision Vaccine Program. What excites you most about the potential to improve human health with the science that's unfolding right now?

Dr. Ofer Levy: Well, as our colleague Stanley Plotkin, who's widely renowned as the godfather of vaccinology says it is hard to overstate the beneficial impact of immunization across the globe. Parents used to be afraid to let their kids swim in the public pool, they were going to get polio. The last time any of us were worried about that. People were dying of smallpox. When was the last time when you traveled anywhere you were worried about that?

Vaccines are a victim of their own success, and we need to realize that. Yes, each new vaccine has to be scrutinized for safety, we have to have the process we talked about. But in the big picture other than clean drinking water, vaccines are by far the most important biomedical intervention known to humans. This in many ways is ushering in a new golden era of immunization, where we can develop vaccines that are more precise, that are safer, more effective, and against a range of indications.

Infectious diseases, yes, we need better influenza vaccines. Vaccine against HIV, we're working in collaboration with the HIV vaccine trials network on that and also against opioid overdose such as Fentanyl. Over a 100 Americans a day are dying of opioid overdose. The

Coronavirus pandemic has worsened to the opioid epidemic, and we are funded by NIH NIAID to develop a vaccine that would induce antibodies against Fentanyl. This would be a vaccine given to people who have substance use disorder. Not to the general population, but they're at risk in a moment of weakness taking a speedy drug that might be cut with Fentanyl. But if they're immunized, they have antibodies in their blood, it binds the Fentanyl doesn't let it get to the brain where it suppresses respiration and causes death.

It's a multiyear project that will culminate in a phase one clinical trial. David Dowling of the precision vaccines program, and I are the PIs and we collaborate with my wife, Dr. Sharon Levy, who directs the substance use program here at Boston Children's. Very multidisciplinary work. We are enthused and excited by the potential of these vaccines.

Mark Masselli: We're watching the FDA authorization for Moderna vaccine and J&J, I think a lot of people want to know, can they mix these booster shots, such as J&J recipient, a booster of Moderna or Pfizer? I know that hasn't fully been vetted yet, but what's your sense of what we might see about blending vaccines?

Dr. Ofer Levy: Hypothetically, it might be very good, you might have additional boosting of immunity, but we need data. As you intimate, we welcome the studies that are ongoing. There are some studies looking at that, and we look forward to the data. But it is an interesting concept, it may be helpful.

I also want to add another thing, and this might not have come across in some of the other discussions. It is not that we had any concerning safety signal about the boosters, it was just the absence of general data. It's not like we saw a bad signal. I just want the public aware of that.

Mark Masselli: Maybe the size of clinical trials probably vary, but people are worried about the size of those clinical trials for the 5 to 11 year olds. How big do those need to be, because the public may not understand the complication of registering people for clinical trials and setting that up. What is the standard size for building confidence?

Dr. Ofer Levy: This is a very good question. It's a question of power of statistical power. And that relates to what are the main endpoints of the study? If the endpoint is the basic safety parameters, and the ability to induce an antibody response that we think is protective, it's possible that a couple of thousand individuals may be sufficient. It also depends a little bit on how big the differences we detect are. On the other hand if one is trying to detect less common events, one might need a larger study. Those are some general principles, yeah.

Mark Masselli: Great. Thank you and your wife for all the work that you're doing.

Margaret Flinter: Incredible, incredible.

Mark Masselli: Sounds like family --- yeah, very impressive.

Dr. Ofer Levy: Thank you.

Margaret Flinter: We've been speaking today with Dr. Ofer Levy, Director of the Precision Vaccines Program at Boston Children's Hospital, and he also serves on the FDA COVID Vaccine Advisory Panel. Learn more about his exciting work by going to children's hospital.org/researchers/Ofer Levy or follow him on Twitter @Levy_O or @PRECVaccines. Dr. Levy, we thank you for your curiosity, your tenacious commitment to uncovering the secrets of immunity and for joining us today on Conversations on Health Care.

Dr. Ofer Levy: Take care and thank you, Mark and Margaret.

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Mark Masselli: At Conversations on Health Care, we want our audience to be truly in the know when it comes to the facts about health care reform and policy. Lori Robertson is an award winning journalist and Managing Editor of FactCheck.org, a nonpartisan, nonprofit consumer advocate for voters that aim to reduce the level of deception in US politics. Lori, what have you got for us this week?

Lori Robertson: In early September, President Joe Biden announced a plan for vaccination mandates for some employers, the specifics haven't been determined yet, but misleading claims about which employers will be exempt have been circulating online. One viral version of the claim list 11 businesses, government branches or federal agencies as being “exempt.” That list includes a mixture of entities that are actually covered under the mandates, some that are not covered, and some that might be covered, but it's unclear without more guidance about the directives.

A taskforce is developing guidance on implementing Biden's executive order requiring federal employees to be vaccinated and separately, the Occupational Safety and Health Administration is tasked with developing a rule for employers with 100 or more workers that would require employees to get vaccinated or get tested at least once a week. We don't yet have those details, but we can explain what we do know about various federal employees.

Employees at the White House and in agencies within the Department of Health and Human Services are subject to Biden's executive order requiring vaccination. That means employees at the Centers for Disease Control and Prevention, the Food and Drug Administration

and the National Institute of Allergy and Infectious Diseases are required to be vaccinated. The order doesn't apply to the legislative or judicial branches. It only applies to executive branch employees. It's unclear whether the OSHA rule will apply to Congress and the federal courts or to independent agencies such as the US Postal Service.

Claims circulating on social media also falsely say employees at Pfizer and Moderna are exempt. Both companies which are responsible for two of the approved or authorized COVID-19 vaccines in the US already require their employees to be vaccinated. That's my fact check for this week. I'm Lori Robertson, Managing Editor of FactCheck.org.

Margaret Flinter: FactCheck.org is committed to factual accuracy from the country's major political players and is a project of the Annenberg Public Policy Center at the University of Pennsylvania. If you have a fact that you'd like checked, email us at chcradio.com, we'll have FactCheck.org's Lori Robertson check it out for you here on Conversations on Health Care.

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Margaret Flinter: Each week Conversations highlights a bright idea about how to make wellness a part of our communities and everyday lives. Vaccinations are considered one of the great public health achievements of the 20th century, reducing fatalities from most common and fatal diseases by up to 99%. But in the 21st century, some of those numbers just aren't stacking up.

As recently as 2009, only 45% of the nation's preschool aged children had received all of their recommended vaccinations and boosters. Researchers at the Children's Outcome Research Program at Children's Hospital in Colorado decided to take an in depth look at the problem.

Dr. Allison Kempe: Primary care practitioners are so overstretched that it's rather impractical.

Margaret Flinter: Dr. Allison Kempe heads up the Children's Outcome Research Program, and she conducted a study on what would help to generate better compliance with required vaccinations, which is a goal of the government's Healthy People 2020 initiative. She found that when parents received timely reminders from their state and local health departments, parents were much more likely to get the vaccinations and boosters for their children that they needed.

Dr. Allison Kempe: What our study did was to centralize those efforts so it didn't take away from the primary care providers, but it helped them to do the reminder recall for their practices centrally, using a state registry. This was much more efficient and much more cost efficient.

Margaret Flinter: Her research shows that one reminder message can be generated for an entire population across communities. It takes the onus and the burden off of the primary care and pediatric practices. Her study published in the December issue of the American Journal of Public Health showed that those effects were pretty significant

Dr. Allison Kempe: in a fairly short six month period in the counties where this was done centrally. About 19% of children who are not up-to-date became up-to-date, versus about 13% in the practice based recall states which on a population level within six months is really very powerful.

Margaret Flinter: The study also suggest that there's a cost savings with a centralized state or county run database and reminder system both in terms of the vaccines themselves and reduce medical cost as fewer children fall ill.

Dr. Allison Kempe: You have one case of influenza haemophilus meningitis can cost tens of thousands of dollars. The costs are of not preventing these illnesses are very high.

Margaret: A state health department driven vaccination program that assist private practices in vaccine compliance for their patient population, improving vaccination rates of young and vulnerable children. Now that's a bright idea.

[Music]

Mark Masselli: You've been listening to Conversations on Health Care. I'm Mark Masselli.

Margaret Flinter: And I'm Margaret Flinter.

Mark Masselli: Peace and Health

[Music]

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