Dr. Mariam Hanna: Hello, I'm Dr. Mariam Hanna, and this is *The Allergist*, a show that separates myth from medicine, deciphering allergies and understanding the immune system.

There are social experiments that happen on a global level that will never again be repeated: the war, the plague, the famine, and the pandemic. Often imitated, never duplicated, I hope.

It kind of feels like parenting. Do you remember, for those with children, how you managed your firstborn when they cried—like even let out a little scream? When a stranger would come to visit, I basically conducted phone screening on them. And how you managed sleep with your first? What happened with your second child?

There's all this information about birth order, but now, as a parent, I actually think it's my parenting order that happened to my next children and siblings.

The uniqueness of these events, however, doesn't take away from the valuable lessons they offer. In fact, in medicine, we often reach back to those moments as offering a key glimpse into a unique, extreme intervention to see how it turned out.

Think back to the crazy things that you did during the pandemic. I quarantined all my Amazon boxes that were getting shipped to my home; I had a little corner for them. I had a system for cleaning groceries, including packaged items that we were going to eat. And yes, I offered virtual care for my patients, who at that time were also too scared to come to clinics and not sure about what they were supposed to do.

That is all the intro I'm going to give you, because this speaker's intro offers a glimpse of what we're going to discuss today.

Today's speaker is a returning guest. Jonathan Hourihane is Professor of Paediatrics and Child Health at the Royal College of Surgeons in Ireland and Children's Health Ireland, Temple Street, Dublin, Ireland, and is past chair and head of department at UCC, Cork.

He was a Fulbright HRB Health Impact Scholar to Children's Hospital Colorado, USA in 2020, which was cut short by—you guessed it—the pandemic. At that point, his wife gave him the brilliant idea for the CORAL birth cohort study of children born in the pandemic. But he himself had the grown-up idea—as I'm just reading you his bio, all that he submitted all by himself—to repeat it in 2025, which is where we've come to the publication now available for everyone to read.

Allergy suits him, as he quotes it, as a field that can be black and white, but the big grey zone in the middle is where he likes to work and enjoy himself. That's really where we find ourselves a lot in the allergy clinic, and the topic of today's discussion.

Professor Hourihane, thank you so much for taking time to join us, and welcome back to the podcast.

Dr. Jonathan Hourihane: It's a great thrill to be back. Having survived the first one, I'm looking forward to this.

Dr. Mariam Hanna: I'm excited to talk about round two because I've often been critical of cohorts—I should tell you that—as to what they can offer.

So let's start with birth cohorts. Do birth cohorts change our natural understanding of allergic disease? Is this kind of how we learn more about this atopic march situation? You alluded to that already.

Dr. Jonathan Hourihane: Yeah, I haven't got a strong answer to say that they do that, but I think the sequence of results from things like the studies in Berlin in the 1980s, up to the EuroPrevall studies in the early noughties, and the Manchester Allergy and Asthma Study, which was somewhere in between that, and then you've got the CHILD Study in Canada, you've got the really famous studies of the CAMP and Inner-City Asthma Studies.

You can make your cohort out of anything to suit your interests and also your capacity to study them. We haven't done any complicated asthma work because we don't have easy access to pulmonary function testing, but as allergists, we've got great access to questionnaires and skin testing. We've done some nitric oxide studies now with our cohort, so we've got some mid-childhood readouts that we never thought we might have at the start.

If you've got your antenna up, people will hear about you and suggest things to you. I think all researchers should be polyvalent or multipathic, able to bring things into their study. If you start out to try and prove one thing, you have a fair chance you won't be able to do it, but if you want to go out and study five things, one of them might come off.

Dr. Mariam Hanna: Multivalent, polyvalent, multipathic—I love it! We're going to add those to the résumé.

Dr. Jonathan Hourihane: I don't know what multipathic means; it just sounded good.

Dr. Mariam Hanna: It's going to be trending, just wait for one moment.

I kind of alluded a little bit, or I read a little bit, as to the thought process behind starting CORAL. Can you elaborate a little bit more about what you were hoping to learn from CORAL? Again, it was such a unique time. Which early life exposures did you think might be impactful, given the time that CORAL was started?

Dr. Jonathan Hourihane: Well, the hygiene hypothesis is on the basis that we're having reduced exposure to viral infections, we're having antibiotics which are altering our microbiota, and family size is getting smaller. The firstborn child is sometimes now 50% of the children in a house, as opposed to 20% or, in Ireland, 10% back in the day. The way families live is different.

Ireland locked down overnight around the middle of March. I'd just got back from Denver, and I think I was still jet-lagged when my wife, Yvonne, had this idea: "If we're going to now isolate children, there's going to be less viral traffic through their environment, and there's going to be less social contact. I wonder, would the allergy rates go up?"

That's what we thought. Our hypothesis was—obviously you have to be a bit more careful—our hypothesis was: "May the allergy rates change?" Question mark. But our sneaking thought was that they might go up.

So we got money out of the hospital. The guy in the room next door in my office building was the guy who gave us €20,000 to just get things moving. I had a research grant that couldn't start, so we had available staff and money, and we got a grant together in the next few weeks.

Mothers with small babies who were locked away at home were recruited and were very happy to join our study. When they came to their first visit after six months, in September, we were out of lockdown but going back into another one.

There were police checkpoints everywhere, and if you said you were going to a medical appointment, you were allowed through the checkpoint. There was some kind of social engineering of engagement with our study that these families were using our visits to have a day out. I think that's great, because lots of families don't like coming to their hospital appointments.

They came to the six-month appointments and had further questionnaires. By the time they got back for their first-year appointment, we already had a new neurologist on our team, and we'd been talking about how some of the six-month-old children had never seen anybody else except their families. Myself and the nurse in the study were the first strangers these children had ever met.

We started doing neurodevelopmental assessments when they were one, and those outputs are just as significant as the allergy outcomes. That took us up to a year, I guess, and we showed that allergy rates were really low for food allergy.

Now, the study only had 350 children, so we have never claimed that it's a population-based study on which we could make a prevalence estimate. We thought we might get more children, but we weren't able to go recruiting in daycare centres, and we weren't able to go recruiting in healthcare settings. We just had to do with what we had.

I think it's an epitome of what's possible when permission is given rather than permission is delayed. It was a facilitated, accelerated process of getting through ethics, and we just started and got on with it, in a way that I think will be impossible now because we've slid back into regulation and documentation for permission rather than forgiveness.

I'm not trying to say we should do research casually, but this was a properly designed study that just got enabled to start because the pandemic was on, and the regulators were also working at home with nothing to do, I think.

Dr. Mariam Hanna: There are so many pearls to pick up from how CORAL was started, including listening to your wife's great idea. I will give her some credit there, which you also did as well.

I want to talk about some of the findings that CORAL found. We talked about less food allergy overall, but actually CORAL initially found more eczema, which traditionally we think is part of the atopic march that does not bode well.

Can we make some comments about the initial findings from CORAL and how those impacted what you think?

Dr. Jonathan Hourihane: We think the eczema rate was probably more or less in line with the secular increase of eczema. We're not saying that's due to the pandemic effect. Because this is an observational, non-interventional study, we will never say that the pandemic caused anything. It's just that we found this in the setting of a pandemic-related birth cohort.

The food allergy rates were low; they didn't increase as my wife had predicted—she's never wrong, so we had to find something else!

Ireland had the lowest breastfeeding rate of Northwestern European countries, or in the European Economic Area and the EU, with less than 10% of babies breastfed to six months, and 50% of babies who left hospital breastfed are no longer breastfeeding after about three weeks.

During the pandemic, the mothers who were, I guess, less distracted by ordinary life—even though they were all still on statutory maternity leave, which in Ireland is six months; it's not like the United States—they were able to breastfeed substantially more than that. More than 55% of the babies were still breastfed at six months, and about 35% were still breastfed at 12 months, which in Ireland is off the charts unusual until now.

There's a longer duration of breastfeeding, a longer duration of exclusive breastfeeding, and much lower antibiotic use. The number of children who had antibiotics by the time they were a year old was only 17%, I think, compared to 45% or 55% in previous birth cohorts.

Hospitalizations were much less, they weren't in daycare, and we were giving them the LEAP-based food allergen introduction advice when they were coming up to their six-month appointment. We were saying, "Don't forget, by the time you come, we're meant to have eaten all these foods."

The rates were much better than they'd been in the Irish birth cohort of note before, called the BASELINE study, which I'd established with colleagues in Cork in 2008 to 2011. The rates were improving over time, and by a year, I think 40% of children had peanut. So that's the CORAL study.

On the neurodevelopmental side, we asked families what the five words were to describe their time as a mother during the pandemic. It's kind of a tragic word cloud: things like "isolated," "challenging," "lonely." Nice words too, but in a word cloud, the big word is the word that's used most often. We've repeated that in our FLORAL study, so we'll come back to that later in the chat, but it was kind of a showstopper seeing how families had to cope.

They had to cope, but they were having fewer antibiotics, they were breastfeeding more, and even when they went back to work, they were still breastfeeding more. The maintenance of breastfeeding to 12 months was significant.

They all got their vaccinations, because that was another medical appointment. Their vaccination rates were almost perfect. The children, I think, were living a little bit more healthily from an allergy point of view, but socially they were getting very isolated.

We'll come back to it again with FLORAL: there were significant social and communication difficulties with these babies because they'd never met strangers. Some of them had siblings, some of them were firstborn, and 25% of them had never seen another baby by the time they were a year old.

For an animal that lives in large groups and cities and socializes with strangers a lot, the idea that a baby would never see another baby is extraordinary, and again, I would say tragic.

Dr. Mariam Hanna: It is. It is.

I often refer to babies as living in the petri dish environment, particularly when it comes to daycare, socializing, and microbial exposures. You also have a recent publication about siblings specifically, so this would impact our patients that had another sibling in the household.

Can we talk about the microbial exposure there and food allergy, specifically in the context of food allergy prevention? I think that one was also an interesting slide.

Dr. Jonathan Hourihane: I'm sorry, I had forgotten about the microbiome, although it's where everything happens, isn't it?

Everybody would know Liam O'Mahony is one of the world's leading—he's probably *the* leading—microbiome in allergy experts, and he works in a major research centre in Cork. When I was moving to Cork originally, he was there, and he left shortly after I arrived. Then when I left Cork, he arrived back shortly afterwards, so it's amazing that we've been able to work together.

We took stool samples of these children at 6, 12, and 24 months, and we showed that children who had breastfeeding, a diverse diet in the first few months of weaning, and had siblings had a more favourable gut microbiome than those who had no siblings. That was helpful.

We've published work recently to show that really it appears the effect is that if the contact you have with other people is with siblings, you have a more favourable microbiome.

The idea from the hygiene hypothesis was that the firstborn went out and had to fight the world, but they also had allergies because they were immune-naive. Their immune system and dialogue with their younger siblings was protective or adaptive for the younger siblings. That appears to hold now.

With this, we can show significant transcriptomic signals in favour of siblings having a positive effect on the favourable microbiome, and an inhibitory effect on, if you like, the clostridial and Gram-negative side of your microbiota.

That might explain the birth order effect or the parenting order that you were talking about. First-time mums don't let anybody touch their child; they interview them at the door by Ring phone! Whereas by the time you're on your third child...

Dr. Mariam Hanna: I was normal! You're making me sound crazy!

Dr. Jonathan Hourihane: Not you particularly, but if you want to take that inference, that's okay! By the time the third child comes along, you leave the door open and hope somebody will come in with food.

I think it has shown us that there is a mechanistic plausibility to that program that's been epidemiologically very solid, but we really hadn't got the grounds for it. I think we have got the grounds for it now.

I've said before, maybe the hygiene hypothesis—which was called the "old friends" hypothesis, talking about ancient bugs and exposures—maybe it should be called the "sibling hypothesis."

Dr. Mariam Hanna: Could be. One of my other comments is often in the Western world, we live in silos, whereas the family dynamic and the extended family dynamic is very different in other parts of the world. Perhaps that impacts as well: parenting style, microbiome exposure, and all kinds of things.

Dr. Jonathan Hourihane: I think that's entirely reasonable, yeah.

Dr. Mariam Hanna: And not to belabour this part too much, I want to talk about two-year findings versus the five-year follow-up, because this is really where things get a little bit more exciting. Well, they were exciting to begin with, but the two- versus five-year findings: do you want to walk us through that first?

Dr. Jonathan Hourihane: Okay, so these children all got released back into the wild in 2022. That was the end of their follow-up after two years, and we said, "We'll be back in touch when the pandemic is over," and that's it.

Once we got back into the real world, we started thinking that the opportunity to do a real-world study in identical circumstances was right in front of us. I got writer's block for about six months; I couldn't do anything with this study, and people kept saying, "How are you getting on?"

I eventually got it over the line, and we got a million euros to set up another birth cohort, which is called FLORAL. Part of the hook for that was that we would capture the CORAL children again, or revisit at five years, to see what their mid-childhood evolution of allergic disease was.

Lo and behold, it's exactly as it had ever been: the food allergy rates stayed low, and the inhalant allergen sensitization rates and asthma went up. It looks like the early life isolation that they had at home hasn't made any difference to what would be the commonest chronic disease of childhood, which is asthma.

We haven't got a strong asthma readout yet because they're only five, so that's why we've done the nitric oxide this year when they were six, and I haven't got that data yet. The early life origins of asthma: not sure. Not sure. I think it's your genes and environment, but I can't say which one is winning or leading that argument.

Dr. Mariam Hanna: Okay, and specifically towards food allergy then? Who's winning that argument?

Dr. Jonathan Hourihane: No real difference in the food allergies from the age of two. Most children who are eating foods at one are eating the same foods at two and five; we've found that. Their food diversity doesn't really change significantly; the major changes are before their age one.

I'm going to get a T-shirt or something to put in some slides stating that I think it should be a major goal of public health that children should be eating the same foods as their parents exactly by the time they're a year old—and no other food. Not pouches, snacks, warm-ups, or Pop-Tarts or anything; they should just be sitting at the table eating the same food as their parents. Whether that's good food or bad food doesn't matter as much as: are they eating the same food as their parents?

Dr. Mariam Hanna: I couldn't agree more with that statement, because I often find my parents here are reaching for the items that have been listed as your "top eight" or "top ten," even though they may not represent the home diet, and by no means are they sustainable allergens that these families are going to maintain in their diet.

So yes, I think there's work to be done on the messaging that we have on early allergen introduction.

Dr. Jonathan Hourihane: And that's at a macro level, Mariam. That's for governments: give your children the same food you're eating. Two hundred years ago, mothers were premasticating food for their babies. If somebody wants a study, that's one to be done! You heard it here first.

Dr. Mariam Hanna: I'm still stuck on it. I need to move my brain faster for you!

With so many exposures changing post-lockdown—and again, I think this is where I get stuck with birth cohort studies or cohort studies in general—how do you break away the effects of what happened during the pandemic in terms of cleaning processes versus the social information versus what was fear-based management that some parents were doing? How do you disentangle that when you look at the data?

Dr. Jonathan Hourihane: There are other parental practices. We asked them bathing frequency, how often they were visiting their doctor, and how often they went to playgroups. I don't know what the national data are for those children in Ireland, but I know from my own children and being a general paediatrician too what the rates and patterns are. They don't seem any different now, having been very different then.

There was no public available daycare until the lockdowns were lifted after the first year. Then the children went back into daycare by the time they were two, and by the time they were two, 45% or 48% of them had COVID.

We had shown—and I don't think this is appreciated much—that lockdown does protect babies from COVID. That's a fact. That's what it was intended for.

The study that we focused on, about what impact that might have, has shown significant results in the fact that it didn't really affect their food allergies or their atopic dermatitis, but it did affect their neurodevelopmental status in the short term.

Then the question is: how representative is it for the general population? That's why we've set up the FLORAL study, because they were born two years after the pandemic was declared over in 2023. They were born in exactly the same months—March, April, and May 2025.

That criticism often happens with studies: were they born with allergies? Were they born at the same time of year? Winter babies get pollen allergy. We were able to eliminate that variable by doing exactly the same in exactly the same hospitals with exactly the same questionnaires.

It's neat and tidy to show that by the time the children in FLORAL—which is the follow-on from CORAL; it's not based on flowers, it's just the acronym—their breastfeeding rates were the

same. That's been a major secular change in breastfeeding in Ireland, so we're very pleased to report that.

Their food allergen rates are probably the same, but with much lower levels of egg allergy because we've got really stuck into the egg ladders in Ireland. I think we've only got one or two egg-allergic children by the time they're a year old out of 350. These are unthinkable numbers! Between 6 and 12 months, they were all on the ladders in a way that I think our study will support the use of that immune-modulating exposure.

They're back to normal rates of hospitalization and antibiotic use, so life has come back to normal in Ireland. The allergy rates haven't increased, but the allergen introduction rates—the rate of peanut introduction by the age of one year is 97%. That's a win!

There's data from America that the rates are changing, and it's changing because advocates like us are reassuring families, with and without risks of food allergy, that the best thing you can do is eat the peanut. Eat the egg, treat the egg allergy, get milk in, and eat everything the same as your parents by the time you're a year old.

Dr. Mariam Hanna: Fantastic. And how does this data compare to other international cohorts? Is it similar? Are there outliers here?

Dr. Jonathan Hourihane: I just have to smugly say there is no comparable international cohort, because we were the only people who established one in the throes of COVID.

We can say that the rates are largely representative of what's been found in Europe before, and much lower than the rates in Australia. We do know that those rates are considered high internationally, and people only use them to get grants. You have to say the food allergy is 10%, and everyone who is reviewing the grants goes, "Well, that's just the Australian data, don't worry about it."

The rates are generally 2% to 5% for all foods, 1% to 2% for each of the major foods, and then the cluster of the rest makes up the remainder. Our study shows that the pandemic didn't affect food allergy rates in any way to differentiate them from historical cohorts.

Dr. Mariam Hanna: All right, time to wrap up and ask today's guest, Professor Jonathan Hourihane, for his top three key messages to impart to patients and physicians on today's topic: the birth cohort study, five years out.

Professor, over to you.

Dr. Jonathan Hourihane: There are three key messages.

Number one is that the COVID pandemic was a natural experiment in extreme isolation, but it didn't affect allergy rates like we thought it might do. But I do think we're getting supportive

evidence, particularly with the reports of social interaction and the microbiome data, that the hygiene hypothesis might need to be revised to give more emphasis to the role of siblings in the education of the immune system of babies.

The second point is that the atopic march to five years of age has not been interrupted or affected by the isolation in the first two years of life. Maybe that's because some of the protective factors that we know about, like breastfeeding and healthy diet, were augmented in a way that balanced the negative effect of lockdown.

The final key message is that it's reassuring from an allergy point of view to know that children's lives have largely returned to normal: infections, daycare, antibiotics. But the allergen introduction rates, as mandated by all our societies and interests into the babies' diets, has become much higher, with near-total introduction of peanut into the infant diet in Ireland, for instance.

Dr. Mariam Hanna: Brilliant. The new normal.

Thank you to Professor Hourihane for joining us on today's episode of *The Allergist*.

Dr. Jonathan Hourihane: It's been a pleasure.

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Thanks for listening. Sincerely, *The Allergist*.