**00:06 Megan Cantwell:** Welcome to the Science Podcast for March 27th, 2020. I'm Megan Cantwell. On this week's show, producer Joel Goldberg gets an update on the coronavirus from Jon Cohen, as well as a rundown on his recent feature about the link between diseases and seasons. And then, an interview from AAAS annual meeting, I speak with Alex Maertens about green toxicology, the movement which seeks to harness non-animal testing methods to manufacture safer, more sustainable chemicals.

**00:36 Joel Goldberg:** I'll now speak with Jon Cohen, a staff writer at Science. We'll be discussing his feature from the March 20th issue of the magazine, An Exploration of Seasonal Effects on Different Diseases, and the sort of research that's being done to identify those effects. Hi, Jon.

**00:51 Jon Cohen:** Hi, Joel.

**00:52 JG:** Before delving into your seasonality feature, I'd like to pick your brain about the present state of the coronavirus outbreak. It's currently Wednesday, March 18, and you've been deeply engaged in reporting on coronavirus for months. At this point, the White House has been addressing the public on almost a daily basis regarding its response to the crisis. Could you describe the United States' response thus far and how it compares to the responses of foreign governments?

**01:18 JC:** Well, each country has gone through a similar pattern of denial, at first, not really wanting to accept what's happening, and very few countries have jumped on it aggressively early on, and each country has to tailor make its own response based on its culture, its governments, its laws. The United States on February 26th, which seems like years ago now, but is less than a month ago, created a Coronavirus Task Force at the White House, and on that day, President Trump stated that there were 15 confirmed cases, and he hoped it was going to be going down to zero. Looking at that today, it's obvious that he was wide of the mark. We stopped hitting the snooze alarm last Thursday. And it was a confluence of events that led to that; one, was that the World Health Organization after long flying against the thinking of many epidemiologists refused to call it a pandemic, but last Thursday they declared a pandemic. We had a beloved and famous actor, Tom Hanks, reveal that he was infected, and his wife, who is well known and beloved, and we had an NBA player who confirmed he was infected, which led the NBA to cancel games, and we had Italy melting down. The measures they've done, and steadily increased, have become more and more restrictive to the point of locking down all of Italy. And that lock down only began in some villages, and then it moved to the entire north, and then it moved to the entire country.

**02:57 JC:** Are we going to lock down cities? Are we going to lock down states? Are we gonna lock down the country? I don't know. The notion from February 26th that we were going to contain this and it was going to go poof was ridiculous. And so, we've had all of these warning signs. We had warning signs, obviously, from China to begin with, but then we had South Korea, and we had Iran,
and we had Singapore, and we had Hong Kong, and we've had one country after another that is ahead of us wrestle with this, and we've been slow to really mount an aggressive response.

03:34 JG: What are the specific responses that are happening right now on March 18th?

03:39 JC: The fundamental priority is to test as widely as you can, to contact people who are in contact with confirmed cases and get them to test, and to have people who test positive isolate. That's one strategy. Then the other is social distancing, which is really physical distancing. And that takes on many different shapes and forms, from closing down big arenas, to closing religious services, to closing restaurants and bars. And social distancing can also be locking down entire communities, shutting them down.

04:16 JG: What tone are you sensing in the many conversations you've had?

04:20 JC: Lots of people are still calling me and saying, "Is this hyped?" "Is this real?" Or, "Come on." Or then, "I just wanna go get my nails done." Or, "I just wanna go out to a restaurant." Or, "I'm really, really angry at this aspect of the government's response." Or, "I'm really frightened, and depressed." "I have a 90-year-old mother, I'm extremely concerned about her and this virus killing her." So I think we've all been going through this process of coming to terms with the reality of the fact that we did not dodge this bullet.

04:55 JG: The modelers, the epidemiologists, really predicted we would be in a situation something like this. I wonder if anybody could have predicted something like Congress discussing a trillion dollar stimulus, or the closing of the Canadian border, maybe in a worst case scenario?

05:16 JC: Well, on February 26th, the presidential press conference I mentioned, Trump was only asking for a little over a billion dollars to respond, and the Democrats had a bill for over $8 billion and Trump said, "Okay, if they wanna give that to me, I'll take it." It shows you how far off the mark the administration was, and this was against the background of the testing kits in the United States that the Centers for Disease Control and Prevention made were faulty. And the top scientists who were advising the White House were saying things that were in conflict with what the White House itself was saying, so there was tremendous confusion.

05:55 JC: What Fauci and others said was that we could launch early phase one studies in a few months, and indeed, we have launched one. But that it would take two or three months to get results from the phase one early trials, which only look at safety and whether the vaccine triggers an immune response. And then, in order to do the real efficacy trial, that would take at least another six months to nine months to get answers, if everything went perfectly well. And then Trump turned that into, "We'll have a vaccine in a year." It's going against science, it's not an opinion, it's not something you can buy, it's not something you can politically muscle.

06:33 JG: I think you just got at an important point too, that maybe people, these past few days more than ever, are coming to terms with. Will this virus, now, not just affect people through the school year, through June, but six months, nine months, 18 months even.
**06:49 JC:** Yeah, I think one of the most frightening things is that no one can answer the question, and there is so much uncertainty right now, it's frightening.

**06:57 JG:** I appreciate you updating our listeners and sharing your knowledge, sharing your experience, because this is weighing on everyone. Why don't we switch gears and discuss your recent feature on disease seasonality? So although your story mentions coronavirus, it's not specifically about coronavirus, but rather the interplay between seasonal changes and many kinds of infectious diseases. That's a pretty popular topic in medicine, in general. One that stretches back to the age of Hippocrates, as you note in your article. But what scientific research has been done to address the underlying nature of this relationship?

**07:34 JC:** Yeah, I coincidentally started working on this story in October, months before this coronavirus reared its ugly head. Because I've written about vaccines for decades and the seasonality of disease is a central topic. Influenza has probably received the lion share of attention. It's such a clear cut winter disease in temperate regions, and it moves between the northern and southern hemisphere each year, in this very predictable pattern. And that's why it's so difficult to tease out the factors that drive it.

**08:06 JG:** What are some of the factors that drive seasonality?

**08:09 JC:** A lot of research has been gone into looking at changes in different aspects of climate. So looking at temperature, looking at humidity, and looking at the dew point. All of it speaks to the idea that at certain times of year, certain viruses or bacteria, or whatever the pathogen is, are going to do better in that environment. And maybe it's summer, maybe it's winter. With influenza, like a lot of viruses, it has a second outer shell, a membrane. All viruses have what's called a capsid that holds them in, holds in their guts. But many viruses like influenza have a second membrane made of lipids, of fats, and it's fragile. And the leading thinking is that these viruses that have fragile outer membranes are more susceptible to changes in humidity. Temperature and humidity certainly correlate with influenza. And temperature and humidity affect things like evaporation rates. And evaporation affects things like the pressure osmotically on the water moving in and out of a membrane, can affect the pH. All of these factors can lead to a virus like influenza being more or less viable. It seems likely that in the winter time, it's a more favorable condition of temperature and humidity. That's one line of research, is looking into these environmental forces.

**09:40 JG:** What are the challenges with understanding these factors?

**09:43 JC:** One of the things that we have to wrestle with is confounding variables. In the United States, we have the Christmas holidays, the holiday season in December. And as one person in my story, one researcher notes, influenza seems to appear when Christmas shopping becomes popular. And of course, that's silly. [chuckle] Christmas shopping doesn't have anything to do with an infectious disease spiking each year. And I focused on the research of Micaela Martinez, who has a provocative theory that she's pursuing, that maybe it's not about the environment, per se, but it's about us, it's about our immune systems. Maybe our immune systems are changing with the seasons.
10:28 JG: And there's that confounding variable that you mentioned.

10:32 JC: There's that confounding variable, absolutely. And how do you separate the chicken from the egg? But it could well be that our immune system has different strengths and weaknesses at different times of the year.

10:46 JG: There's a lot of variability when it comes to what diseases are most prevalent season to season and region to region. Could you talk about that variability?

10:55 JC: We know that polio is a summer disease, and respiratory syncytial virus is a winter disease, flu is a winter disease. Chickenpox comes up in the spring. Rotavirus is in the winter. And we also know that different regions of the world have different experiences with viruses, whether they're temperate regions or subtropical, seasonality is linked to rainy seasons for mosquito vectors, let's say. But there are all these odd things that it's hard to figure out why does Hepatitis C peak in the winter in India, but in the spring or summer in Egypt or China or Mexico? And the research that has gone into understanding this phenomenon, it hasn't been that rigorously studied, but it's extremely difficult to tease out the factors that drive seasonality.

11:45 JC: So, let's take rhinovirus, the common cold virus. Turns out there's a study in Scotland that finds it does not have a membrane, that outer membrane like influenza or coronaviruses. It's around 87% of the year, it's always around because it's viable all the time. There's nothing that slows it down. And also because we don't have widespread long-lasting immunity to these cold viruses. Now, it could be because of mutation rates of the virus, it can be that there are many strains of those viruses circulating around. Why does polio occur in the summer time? No one knows. I don't know. And I think that's true for most of these viruses.

12:28 JG: Bringing our discussion full circle, why is disease seasonality research so important to understanding and adapting to the coronavirus pandemic?

12:37 JC: The coronavirus that causes the new disease we're seeing, we don't know whether it's going to be seasonal, it hasn't been around long enough. And the seasonality issue, many people struggle with understanding this, the analogy I use is like a car, it's not as though when spring and summer time comes around, the key comes out of the car and the engine doesn't run. It's more like the gas pedal and you take your foot off the gas pedal, so when spring and summer comes around, influenza virus can still transmit in that time period, but it doesn't during those seasons, because so many people in our population are immune that it can't keep going from one person to the next, and make a chain that creates an epidemic, so it dies out.

13:25 JG: Could you kind of describe what you mean by dies out?

13:28 JC: It's a simple truth of epidemics. For an epidemic to become an epidemic, each infected person must infect at least one other person, or over time in a population, it won't sustain itself, it will peter out. If you imagine a game of tag, if somebody doesn't tag someone else, the game's over. It's a balancing act. Seasonality has an impact on the transmission rate, so does the immunity in the population, ultimately, because if a lot of people are immune, the virus has no where to go, it has
fewer places to go and you drop below one. That's the point.

**14:06 JC:** There's a study that shows that people respond to influenza vaccine differently at different times of the day. What if to get a powerful immune response against any virus that we have a vaccine for, it works much better to do it early in the morning. If we have a seasonal pattern to COVID-19, to this new coronavirus, we need to know when to do the vaccination. The influenza vaccine we use, it doesn't last very long, the immunity triggered by the vaccine only lasts a few months, three months maybe. Well, if the coronavirus that we're battling now has the same seasonal pattern as influenza, we need to know when to do a vaccination campaign. If you do it too early, it's not gonna do anything. If you do it too late, it's not gonna do anything. So that's one of the central questions that if we can answer it and better understand the seasonality of this new virus, we can better combat it with tools like vaccines.

**15:08 JG:** And as scientists search for that vaccine, people will be feeling immense stress and anxiety about the future. Is the long term as harrowing as it seems?

**15:17 JC:** I do wanna stress something, we're gonna get through this. It's not the deadliest disease I've ever covered in my life. It's not the worst possible case scenario. It's bad, it's especially bad for elderly people and for people who have heart disease or diabetes or hypertension. I think I'll be okay. I think my wife will be okay. My three kids, I'm not really worried about their health. Some of them may not even have symptoms, but I'm worried about the community and I'm worried about the world. It's exacting a huge toll. The upside is that we have an opportunity to come together like never before, because the world has never had one common enemy. There is no country that loves this virus or wants this virus. Science is where the hope lasts of solving the problem. It's not simply about waiting for the virus to finish its way with us. It's about us taking action and making smart decisions about how to stop it.

**16:12 JG:** Jon, thanks so much for taking the time to speak with us.

**16:15 JC:** Yeah, you bet, Joel.

**16:17 JG:** Jon Cohen is a senior correspondent at Science. You can find a link to his disease seasonality story at sciencemag.org/podcasts.

**16:27 MC:** Stay tuned for my interview with Alex Maertens about green toxicology.

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**16:37 MC:** I'm here at AAAS annual meeting with Alex Maertens, a junior faculty member at the Johns Hopkins Center for Alternatives to Animal Testing, and also the director for the Green Toxicology Initiative. She gave a talk today on a panel about green toxicology, the movement which seeks to reduce hazardous risk in chemical product design. Thank you so much for joining me, Alex.

**16:58 Alex Maertens:** Thank you, glad to be here.
17:00 MC: I wanna start with the chemical that your talk was focused on, which is bisphenol A. What were the toxic effects that led researchers to want to develop a different chemical?

17:10 AM: So, ironically, we don't even really know the answer to that question. When bisphenol A was first discovered, the person who synthesized it thought, "Well, maybe this triggers the estrogen receptor," tested it, and it was very weak. So because of that, they assumed that it really didn't have any estrogenic potential, it was manufactured. The concerns about endocrine disruption really came later. I would say that the data really aren't clear on that. We do know that it has some biological effects. There's a lot of debate about what doses, about what affects those are. And as I mentioned in the talk, there's been an enormous amount of study on it, like I said, over 10,000 PubMed extracts on that. The exact molecular mechanism is probably not clear, even today.

17:48 MC: Despite not knowing the exact molecular mechanism, they forged ahead and created an alternative, which is bisphenol S. Could you talk about what was the difference between bisphenol S and bisphenol A?

18:00 AM: The assumption was, "Alright, it's finding the estrogen receptor, that's an easy fix. If we add a couple of molecules onto it, it won't have the same structure, and it will not bind the estrogen receptor, so we have solved the problem." And I should emphasize that a lot of the push to get an alternative to BPA was not because there was a regulatory directive, but consumers wanted a label that said BPA-free. Of course, now that we have a better understanding of the many types of receptors out there, we know the BPS, the replacement, actually triggers a lot of the receptors that we think BPA probably is, and it does so much more potently. So, it's not clear that we've made a good substitution or a regrettable substitution, in the case of that chemical.

18:38 MC: Part of it was that the testing wasn't getting at the actual molecular mechanism behind what could have been the problems with this toxicity. Are there approaches that are a way to get at the molecular mechanism?

18:50 AM: Yeah, I think traditionally when we were testing chemicals for regulatory purposes, the typical approach was to look at the effects in rats and say, "Well, okay, the effects happened at 50 milligrams per kilogram, we'll make a couple of adjustments to that to make sure it's safe," and then, that's what we said. In the case of BPA, it did come up with a fairly conservative dose, and again, that was, I think, based on reproductive and developmental concerns, but this didn't really capture what was causing it. At the end of the day, if you have some sort of outcome from a rat, that doesn't tell you what receptor was being triggered to cause that. And if you don't know what receptor was being activated or what molecular event is happening, you can't really fix that problem. So we refer to animal assays as black box assays. You get an answer, but you don't get the string of events that led to that. One of the things that we try to do with the Center for Alternatives to Animal Testing is develop assays that can kinda answer these questions quickly and more cheaply and ideally without the use of animals. For example, in my work, we use a lot of transcriptomic data, data on gene expression, to try to figure out, based on that, what is the likely molecular mechanism? And our own research indicated that for bisphenol A, especially at low doses, it was not the estrogen receptor, it was other related receptors.
20:00 MC: What are the current limitations to these computational methods when it comes to testing the toxicity of chemicals?

20:07 AM: Well, one of the papers that we just got accepted, actually, we tried to study how many genes that were implicated in the progression of cancer were poorly studied. So we basically just looked at how many of them had very few articles on them, how many of them were known to be involved in a certain pathway, and the answer was really surprising. It turned out that 80% of the genes that are associated either with survival or with the glycine index and prostate cancer, for example, 80% of those genes had almost no information. So I think that one of the important things to consider when we're trying to design alternative assays is to keep in mind how little of the map just really is terra incognita, how much of it we just really don't know. So I think that it's important to be a little bit humble and keep in mind that there's just a lot of biology, a lot of basic biology that still needs to be studied.

20:56 MC: So this different way of figuring out why a certain chemical is toxic, is this being incorporated into other aspects of the industry, or do you think it's still kind of at a starting point?

21:09 AM: It's very much still at a starting point. I would say that you do see some use of it by industry, especially the pharmaceutical industry, they're fairly sophisticated because the costs of failing are extremely high. And in the case of hazard assessment for consumer and industrial chemicals, you are starting to see that in industry because the cost of getting it wrong are going to eventually be high, but it is expensive to do, and it doesn't necessarily give you something that you can take to regulators. So if I show up at EPA with a transcriptomic study saying, "Look, my chemical is safe," well, EPA isn't used to that, they're used to seeing rat studies. So they don't necessarily require but that is the default approach. They've been trying to get away from animal testing, and they have a very... Recently announced an initiative for this, but the roadmap to getting there isn't clear. And when they do have concerns about industrial chemicals, for example, the rat test or whatever other animal test is usually the first choice.

22:02 MC: Is there a way to not have animal testing at all or do you think it'll always play some role in testing for toxicity?

22:07 AM: I think that we can very quickly get to a point where very little animal testing is used, we can prioritize our chemicals better, we can roll out some risks very, very quickly. I think, are we ever going to get to a point where the computers give us all the answers? That's going to be very difficult. There's always going to be a certain complexity to biological organisms that's going to be difficult to get. I do think we have to be mindful of the immense gap between what we know and what we would need to do that. One of the things that people haven't been considering is that there's an enormous amount of human data that is available, if we just captured it. People always say, "Well you can't test chemicals on humans," and that's true. But once a chemical is being used in cosmetics, it is being tested on humans. A lot of the hazards that we picked up recently. So for example, concerns about trans-fatty acids, that was not picked up with animal testing, that was picked up with epidemiology testing, looking at, "Look, there's some correlation here between trans fats and exposures and heart attack." We would never have picked that up with animal testing, because we wouldn't have even known to ask the question.
23:08 MC: Do you think by incorporating more ways to study the molecular mechanisms, this could potentially catch those more stark side effects?

23:18 AM: The risks or the hazards that we're not detecting now are probably not the really bad ones. There are probably things that just are shifting the curve a little bit. So for example, one of the reasons that lead toxicity was difficult to pick out, because it wasn't causing, except at very high doses, really obvious neural problems, it was just shifting the IQ range a little bit in the direction you don't want it to go. And it's very hard to convey how serious that is, but that is very, very serious because it just looks like statistics, it just looks like a graph changing, but there are people...

23:50 MC: Involved, right.

23:51 AM: Yeah, and if your IQ would have been 110 and now it's 95, that's going to have very severe consequences for you for the rest of your life, and it's going to have consequences for society. And those sorts of hazards are very difficult to capture in animal tests, because you'd have to have a lot of them and look at them over time and look at very, very sensitive end points.

24:10 MC: And that was one thing that you brought up in your talk, which I thought was really interesting, was that a solution doesn't necessarily mean that there's no side effect, no impact, it's about which trade-off is better.

24:22 AM: I think that's very important for people to keep in mind because I get asked all the time, "Well, what's a non-toxic chemical?" And of course, my response as a scientist, is like, "That's a non-question." All chemicals are toxic at some dose. In order to kind of go forward, we have to be a little bit more realistic about what it means to live in a universe of chemicals, some of which hurt us, some of which don't. So for example, with caffeine, it is a neurotoxin at some level. That's why we drink it, it acts on our nervous system and causes some side effects, but we have all decided that we like those side effects even if it keeps it up a little late, because it gets us through our day. Certainly, in terms of the epidemiology studies, the worst you can say about coffee is you don't wanna drink a whole lot of it while you're pregnant, or if you have a predisposition to heart disease; other than that, it appears to be a net benefit. So that's the kind of trade-offs that we're realistically looking at. It'll have some effects, some good effects, some bad effects. We just need to kind of ask those questions at a better level.

25:12 MC: It's kind of hard to get that nuance across, I would say, to consumers and the general public, sometimes.

25:18 AM: It is. My experience is that what most people wanna know is, "Is this going to give me cancer tomorrow? And the answer's usually no. But I think, yeah, there is this perception that there's all these terrible chemicals out there, and they're going to cause cancer and what can they do to stay safe? And to me, that's the wrong question to ask.

25:32 MC: Part of the movement of green toxicology is front-loading more of these studies. Do you think that some people in industry will be a little hesitant if it does increase the timeline for the conception of a chemical to it being in the market?
25:48 AM: I would say that the opposite is true, I think industry is pretty excited about the idea of being able to do this more quickly and better and at earlier stages. One of the things that kinda got me interested in this is I used to work with a lot of research and development chemists, and they were really frustrated that they could go into the lab and they could design this super cool molecule that had this great property that you were looking at. It was a sealant or it was some sort of coding that was gonna be better than anything else out there, and they thought they'd done their job. And then the toxicologist shows up. [chuckle] And says, "Yeah, this is a carcinogen, go back to the drawing board." And to them this was very frustrating. And even worse, is if you've put tens of millions of dollars into developing this and then you gotta wait for a two-year assay in rats to figure out if this is or is not gonna be accepted. Well, that is not what industry wants. I think the problem is, is that there's a concern about a lot of these more sensitive assays have more noise in them. And they don't want that to become sort of a public relations problem.

26:46 MC: But it seems like there is general agreement that incorporating these methods will both be better for industry regulation to catch things earlier, and also, it's less money as well, it's less money and less resources since you need less of the chemical to test it, since you aren't doing it with animals, you're doing more of a computational method.

27:07 AM: Exactly. If it worked perfectly, I don't think that there would be any concerns. And then, we would've already adopted it. But the reality is, if you ask people, "Well, do you wanna test chemicals computationally without animals?" The answer is yes, but then if you say, "Hey, guess what, most of the chemicals that you're using, they haven't been tested for safety in animals," people are horrified to discover that. So until we close that gap, until people are comfortable saying, "Yeah, we ran this through all of these in vitro assays. It looks reasonably safe. Be mindful of the fact that nobody can guarantee something is completely safe because that is never going to be possible." Animals or not, that's just a limitation of being humans in an uncertain world. That's always going to be an issue. I think there's an enormous amount of work we can do to try to understand better the types of ways that biological systems can be disturbed, what are the molecular mechanisms that caused that, and what we can do to design that out of modern chemicals.

28:01 MC: Thank you so much, Alex.

28:02 MC: That was Alex Maertens, director of the Green Toxicology Initiative at Johns Hopkins University. You can find a link to her session from the 2020 AAAS annual meeting at sciencemag.org/podcasts.

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28:15 MC: And that concludes this edition of the Science podcast. If you have any comments or suggestions for the show, write to us at sciencepodcast@AAAS.org. You can listen to the show on the Science website at sciencemag.org/podcasts. There you will find links to the research and news discussed in the episode. You can subscribe on iTunes, Stitcher, Spotify, Pandora and many other places. This show was produced by Joel Goldberg and Megan Cantwell, and edited by Podigy. Jeffrey Cook composed the music. On behalf of Science Magazine and its publisher, AAAS, thanks for joining us.