Transcript

[00:00:00] Manon Cox, M.D., Ph.D.: It is interesting because I've been hearing the other side of this, that this virus, Omicron, is actually causing such low severity in healthy adults that some people say this is a perfect live-attenuated virus, and therefore it would be a good thing to have many people being infected with the virus because now you're going to have natural immunity that is a little broader than the spike protein only.

You would have a broader T cell repertoire that could protect you against future variant viruses. I wouldn't say, "Hey, let's get everybody infected." No, I would say, "Make sure that the people who are immunocompromised know that they are in the risk groups, and that they should continue to be cautious. Younger people that are going to be able to deal with this pretty well, just have them go out and let them indeed get exposed."

[00:00:59] Marthe Haverkamp, M.D., Ph.D.: Welcome to the next episode or for our podcast series on the COVID-19 pandemic. We will discuss Omicron, what it means for the state of the pandemic, the future of vaccines, and how to balance mitigation measures with what our society can still tolerate. I am Marthe Haverkamp, Senior Director in Healthcare Industry Group of Alvarez & Marsal, and I am delighted that you have joined us for this special podcast featuring two international COVID-19 experts, Manon Cox and Ab Osterhaus.

Professor Osterhaus is a world-renowned Dutch virologist, now with his lab at the University of Veterinary Medicine in Hanover, Germany. His research group discovered many viruses, among others, the human metapneumovirus. Ab was first in 2003 to irrefutably prove that SARS was caused by coronavirus. He has authored more than 1,300 peer-reviewed papers, but also started several companies, two of them being CROs, and the other developing treatment and vaccines against metapneumovirus. Manon Cox is CEO and Co-Founder of NextWaveBio.

She started that company in 2018, and helped biopharma companies in drug development and manufacturing. Before, Manon was President of Protein Sciences, leading the development of an influenza vaccine, Flublok, that received FDA approval in 2013. The company was acquired by Sanofi years later. Manon has a PhD from Wageningen in the Netherlands, and also an MBA from Nyenrode Business School. I am very curious, Ab, how for you the arrival of Omicron changed your perspective on the pandemic, and the animal models with reduced inflammation in the lung and their severity. Do you feel optimistic about what is to come?

[00:02:59] Ab Osterhaus, Ph.D.: I'm rather skeptical at the moment. Basically, we got this new variant some time ago, and so we are running through the whole alphabet. The alphabet, the gamma, delta, et cetera. Now we have arrived at the Omicron. It has become a variant of concern. Also WHO is very concerned about it. As a matter of fact, the spreading of that particular virus was really much faster than we have seen with the previous variants, like the Delta variant, which is the last one. The idea was therefore also that it was going to take over from the Delta variant, which has happened in many countries in the meantime. This was the bad news.

The virus is really spreading very fast. The good news is that what we are seeing today is that the disease severity that's associated with the infection, for several reasons, seems to be much lower, or at least lower than what we see in the previous variants of concern. The only problem is that that when we look at the overall picture, obviously, is more and more people get infected, and especially people with preexisting conditions, and elderly people, people with diabetes, people with heart transplants, et cetera. These people they do get sick.

Now, once the virus is spreading so fast, we see that if they come all within, let's say, a couple of weeks instead of a couple of months, then the hospitals are going to be overwhelmed, or the whole system from GPs all the way to intensive care. That's what we are afraid of at the moment. I'm not very optimistic as long as we do not have a vaccine that is adapted to the new variant. I think it's tricky because the protection that's being provided by the vaccines that we are using today is not long-lasting and not very solid.

[00:05:07] Marthe: In fact, what you're saying is that a big group of immunocompromised, and that of course also in the US that was 7 million I think, people who do not have a strong immune system, that that is the main group that should be worried now.

[00:05:21] Ab: Yes, I think that's the case. We see a lot of breakthroughs at the moment, so people who really get sick-- The big problem there is also that when you look at the personnel in the hospitals who really have to attend the people coming to the hospital, we see a lot of infections there as well which really reduces the hospital capacity again.

[00:05:43] Marthe: Do you think that the fact that this variant spreads easier, but is less serious, does that predict anything about next variants that are coming up? What to us, that something comes up that spreads easier, but that is either worse than Delta?

[00:05:58] Ab: Everything is possible obviously. It really also has to do with the evasion of the immune system. We know that phenomenon from Influenza viruses, and of course we get to a certain level of herd immunity based on T cell responses mainly, but sometimes you get variants like we had in 2018, Influenza variants that really are much more severe than previous ones. There is a tendency that it becomes milder, but that's not a safe thing to assume. It might well be that you get new variants as well that will pop up and cause more disease, and even go faster in the population.

[00:06:40] Marthe: Yes. The influenza, that's also your area, Manon. What do you think?

[00:06:45] Manon: It is interesting because I've been hearing the other side of this, that this virus, Omicron, is actually causing such low severity in healthy adults. That some people say this is a perfect live-attenuated virus, and therefore it would be a good thing to have many people being infected with the virus, because now you're going to have natural immunity that is a little broader than the spike protein only, and you would have a broader T-cell repertoire that could protect you against future variant viruses.

I was reading an opinion ads in Australia by Gary Groman, who used to be the vaccine reviewer at TGA, the Australian FDA. He basically states the best protection is there for people who have been vaccinated and then had a breakthrough infection with Omicron, not with Delta, but with Omicron, because there's apparently lab data that shows that if you look at the immune response in those individuals, they are very-- that appears to be extraordinarily broad, that they are broadly protective against all the previous variant. I was wondering whether you've already seen that.

[00:07:59] Ab: I appreciate what you're saying. It's an opinion you hear much more often. It could well be that indeed this mitigated virus, so to say, creates a certain level of herd immunity, but that's not the whole story. I fully agree with you that the T cell response against the other proteins of the virus can be quite important, but there's also a genetic factor there. We have also seen susceptibility genes in the meantime. Some people don't get sick at all, whereas others get very ill. There is the whole range there.

What you really have to consider that undoubtedly everyone in the world will be infected by SARS-CoV-2. If that is a mild variant, you're happy, but there's always a segment in the population, in our population that's about 10 to 20% who are immunocompromised, and in those individuals, that really even this small wimpy virus can cause quite severe symptoms. For the time being, if you get it in a very short period of time, you get so many infection due to the more rapid spread of a more attenuated virus than still you enter into a situation where hospitals and the healthcare system cannot cope any longer.

[00:09:20] Marthe: Just to recapitulate for the listeners. What you say, Manon, is in fact we should take advantage of this current situation where Omicron seems to be less severe. Why not get everyone infected so we all mount at least some immune response that will help us later now that it's less dangerous to get COVID? Then you say, Ab, that is fine, but there is so many people that are immunocompromised. All these people will overwhelm hospitals if they get infected right away, because infection is the flu, that's always been the case. Vulnerable people have always been at risk for severe disease and hospitalization, and death.

[00:10:01] Ab: It's a very similar situation. We have herd immunity against flu, because we have this T cell response against the internal proteins. Still, when we get the serious season of flu outbreak, there's a lot of people who go to hospitals and who die. They're mainly in the risk group. Not all of them, because there are some people with a higher genetic susceptibility for whatsoever reason. On the one hand is the immunocompromised, and on the other hand is the people who are more susceptible.

Then again, at the end of the day, I agree with Manon that this virus will basically infect the whole world, every person in the world. That does not mean that all these people are immune to the infection, because if it would be like, for instance, a systemic infection like measles then you have a completely different situation. You get much better protection for life even.

With the respiratory viruses, be it influenza, be it RSV, you get a very temporary protection. That's what we are seeing quite clearly now also with the different variants of the SARS-CoV-2. We see that after three, four months, the current vaccine does not protect against Omicron. Basically, people vaccinated, but most of the people who are vaccinated, they have been vaccinated more than six months ago, and these people they get perhaps not a full-blown disease, but they get a lot of disease, plus the virus spreads like hell.

[00:11:26] Manon: Doesn't all this point towards maybe to really better educate and better communicate about this virus, right? Because I totally agree that you need to protect the people that are vulnerable, but we will only reach broader immunity in the population if there

has been exposure. I wouldn't say, "Hey, let's get everybody infected." No. I would say, "Make sure that the people who are immunocompromised know that they are in the risk group and that they should continue to be cautious.

Younger people that are going to be able to deal with this pretty well is have them go out and let them indeed get exposed. Again, only time will tell. Here in the United States we see stadiums full of people. You can be assured that there's going to be super spreaders amongst those people that are in those stadiums. We're going to see what will happen. How this will pan out.

[00:12:30] Marthe: If you were the President you wouldn't have installed a mark down in the US as the Netherlands has done?

[00:12:37] Manon: If I was the President, I would have definitely not done that. I think it's a wrong decision. I know that I'm very much in disagreement with Ab there who has continuously talked about strong lockdowns. I just don't think it's the right thing to do.

[00:12:51] Marthe: Ab, what do you think?

[00:12:53] Ab: I profoundly disagree obviously. For instance, they'll only hear about the children in the Netherlands. You have this argument now, the virus is circulating amongst the children, and because it's so mild in children, if you see how many children get severely ill, how many children die, is much more than in flu. It's three times as many at the moment.

I think you have to be very careful there. I think what you are saying, that sounds very nice, but if you look how many people, in spite of the vaccines being there, die every year still from flu and COVID is much more severe. Until we have reached the situation this flu, and we are not there at this stage for sure, and it may take one, two, three, we don't know even how many years before we are there, we have to be very cautious.

[00:13:43] Marthe: But you are in agreement on vaccinations, vaccination mandates, for example, in domestic flights in the US? What's your idea there?

[00:13:51] Manon: It should be a free choice. Having access to vaccines is a right. I definitely think that if people would realize that the disease, COVID, in and of itself is much worse than the risk of vaccination, at least that is the way it looks at this moment in time, and that's probably even true for Omicron. I do know people that were not vaccinated that got COVID and they were in far severe states than people that were vaccinated. When I talk about breakthrough and opening up that has to do, you need to see that in combination with the last proportion of the population that has already been vaccinated.

[00:14:31] Ab: I think basically, I would agree to a certain extent that vaccination can get us out of this, and basically communication, telling the people what's going on. This is extremely difficult to do that. If we were in a similar situation with flu where we have a mismatch of the vaccine, we know that the vaccine protection goes down from 60, 70% to only 10, 20% and even being absent. We are in that situation with the Omicron at the moment, everyone should be free to be vaccinated. Yes or no. It's your own free choice, but to have the freedom to go into a stadium, to go into an airplane, all these kinds of things that can be, that can be restricted.

That's all in the game. I think we should not allow people who have not been vaccinated, we should not allow them in restaurants, in places where a lot of people get together. Still people can refuse to be vaccinated. There is an indirect obligation to get vaccinated. If you don't want to be vaccinated, well, it's not that bad not to go on a plane or not to go to a

restaurant. It's fine. At the moment it's like that in Europe. If you take a flight, wherever you go, it's even if you've not been vaccinated, you don't get on the flight.

[00:15:49] Manon: In the United States, actually people that have had a natural infection are not being recognized as also being immune. It would probably be good because they are-- Personally, my situation is I had two Pfizer vaccines. I got a breakthrough infection because indeed the vaccines are not as good as we would like them to be. That breakthrough infection does not count as a booster. I'm thinking that I'm better protected than just getting that booster, but I'm basically being forced to take the booster because it is not being recognized as a superior vaccine, my breakthrough infection.

[00:16:36] Ab: Just realize what would've happened to you if you would not have been vaccinated. That might have been a very severe situation. It's very difficult, and I agree with you that infection as such might be considered as, and that's what we have in most European countries, that the infection counts just as much the vaccination.

[00:17:00] Marthe: You mean infection as a booster, but you do still need a booster, no, to be fully vaccinated?

[00:17:07] Ab: That's correct, but it only lasts for three, four months, which again is very similar to what you see in influenza. Now, if you look at, especially if you look in elderly people, one of the big problems is many people have themselves vaccinated in September. Then if the flu hits in April, they are not protected anymore. It's a very similar situation that we're going into.

[00:17:29] Marthe: What do you think? Will there be fourth dose and then a fifth dose?

[00:17:33] Ab: I think it's difficult to predict what's happening because coronavirus, they do mutate very fast. Basically I would not be surprised if at the end of the story, it will be that we get the combi vaccine where we have the flu strains present, we have RSV, and then we also have COVID, and that you get a cocktail there. In one go, a cocktail for the winter respiratory disease for the risk groups at the end of the day. I think that's what you're going to see at the end of the day, it'll mitigate, because there's enough immunity in the population. Then that's where we're going to end. With flu we are not even there because we get pandemic after pandemic. Every 20, 30 years we have a pandemic.

[00:18:16] Marthe: Researchers worked on mRNA vaccines for years, but then why did they never work before?

[00:18:24] Manon: There was quite a lot of work done, and they just never cut it. They never were as good as the vaccines that were already available for influenza to protect you from influenza. We really don't know. I think the reactogenicity of the mRNA vaccines is still very high. I would prefer to have a vaccine that has lesser reactogenicity.

[00:18:47] Marthe: You mean that side effects when you just get the vaccine.

[00:18:51] Manon: Yes. Then long-term, we really don't know too much about this. I know that you're interested in what is the long-term, with the long-term, we'll only know two to five years from now by looking at big population data. We will never know for sure, because there are no good controlled clinical studies being done.

[00:19:11] Marthe: Do you think that there are lessons that we have or positive things that we can learn, or that we did learn from this pandemic that we can bring forward?

[00:19:21] Manon: The good news is that we have learned and that we have seen that we can have vaccines that can be deployed and developed very rapidly. That was great.

[00:19:31] Ab: That's a very positive message, and that we have also learned that we did not do a good job in terms of producing antivirals. Which could have been done, and we should do immediately now against all the big virus groups like the coronavirus, the influenza viruses, the paramyxoviruses. We should just develop these things in peace time.

[00:19:53] Marthe: Do you believe in the Paxlovid, the Pfizer--? It seems to be so ideal, right. Indeed if you take it in the right. time frame in the beginning, and then there's too much side effects and it's so effective. How do you think it'll play out in the real world?

[00:20:08] Ab: I think the first data are a bit too optimistic. If only it's 50% of what it promises in the clinical trial, then still is good enough. It's again, like with the anti-flu drugs, if you don't get it within 48 hours, virtually all the benefit is gone. What you need to do is to have a good setup. The same is true for the monoclonal antibodies. The GSK monoclonal still works.

Are you against the Omicron? If you give it within 24 hours after diagnosis, you get, let's say 70%, 80% reduction of hospitalization, if you use that in high-risk people. The Paxlovid is the same. If you give it in the hospital when people are already hospitalized, because that's what they do with the monoclonal antibodies, your effect is less than 2%. We know that. Really, how to set up these kinds of things and how to implement it. I think it can be a game-changer.

[00:21:03] Marthe: Thanks so much, both Ab and Manon. We're at the top of the hour. I feel we touched a good balance of, on the one hand, signaling the more endemic aspects of the pandemic currently, on one hand, but on the other hand, also the cautious measures we 2have to take. Thank you to our audience for joining us for this podcast today. Manon and Ab, we'd like to thank you for taking the time to share your knowledge with our listening audience. To listen to our other podcasts, please visit us at alvarezandmarsal.com. Thank you again, and talk more soon.