Important Clarifications Regarding Covid-19 and Natural Medicine

By: Heather Zwickey, PhD, Natural Medicine Journal

Dispelling myths and misconceptions

There has been some misinformation circulating regarding Covid-19 and natural medicine. On this episode, critical questions regarding Covid-19 are answered by immunologist and integrative health expert Heather Zwickey, PhD. Zwickey is executive program chair and a professor at National University of Natural Medicine in Portland, OR, who also has specific training in infectious diseases.

Heather Zwickey, PhD, earned a PhD in Immunology and Microbiology from the University of Colorado Health Sciences Center with a focus on infectious disease. Zwickey went on to complete a postdoctoral fellowship and teach medical school at Yale University. At the National University of Natural Medicine in Portland, OR, Zwickey launched the Helfgott Research Institute and established the School of Graduate Studies, developing programs in research, nutrition, and global health, among others. She currently leads an NIH funded clinical research training program. She teaches at many universities and speaks at conferences worldwide. At Helfgott Research Institute, Zwickey applies her immunology expertise to natural medicine, with specific interest in the gut-brain axis in neuroinflammation.

Transcript

Karolyn Gazella: Hello, I'm Karolyn Gazella, your host and the publisher of the *Natural Medicine Journal*, a peer-reviewed online journal for integrative healthcare professionals. There's been some misinformation circulating regarding Covid-19 in natural medicine. Today we're going to clear up the confusion as much as we can. Perhaps the most troubling are the claims being made on the internet about natural cures for Covid-19, but that's just one of our topics today. On this episode, critical questions regarding Covid-19 will be answered by immunologist and integrative health expert Dr. Heather Zwickey. Dr. Zwickey is executive program chair and a professor at National University of Natural Medicine in Portland, Oregon. Dr. Zwickey, thank you for joining me.

Heather Zwickey, PhD: Thanks for having me.

Gazella: Well this will be great because this is kind of an update and an extension of what we did the last time we were talking and a lot has been happening in this area, but before we dig in, for our listeners who may not be aware of your expertise, do you have specific training in infectious disease?

Zwickey: Yes. I did my PhD in immunology and microbiology in the 90s and my PhD was actually working on vaccine technology for tuberculosis. I was working on how to get the immune system to respond to this deadly microbe, and at the time I got additional experience working with HIV and smallpox and some other fairly terrifying infectious agents. Since my

PhD, I've been teaching immunology for more than 20 years and I've also taught medical microbiology. While I had the opportunity to work on Ebola virus at the NIH, I decided I was too accident-prone to do so, so I stayed away. But yes, I have quite a bit of background in infectious disease biology.

Gazella: Perfect. I knew you were the perfect guest to have on with us and you, of course, are on our editorial board for the *Natural Medicine Journal*, so we appreciate that. Now we have a lot to cover, but my first question is perhaps the most important as we frame our conversation today. Are there any natural medicines in the form of vitamins, minerals, herbs, or other nutrients that have been shown in human clinical trials to prevent or treat Covid-19?

Zwickey: To date there has been no research specifically on Covid-19. The conventional medical community is working as fast as they can testing the antivirals they have against this specific microbe, and we in the natural medicine community should really be doing the same, but unfortunately we don't have the resources, specifically meaning most of our institutions don't have bio level safety for facilities, so we've been unable to test natural medicines against Covid-19.

Gazella: Yeah, that makes a lot of sense. Now I know a lot of our listeners have to explain to patients why this virus is different from the flu virus, which can also be deadly. So just remind us what's the difference between Covid-19 and the typical cold and flu virus?

Zwickey: Yeah, I think this is a really important distinction. And you could ask the same question of what's the difference between Covid-19 and an average Coronavirus infection. One of the things that makes a virus specific for a particular tissue is its spike protein. Remember that the spike is why one virus like flu is going to bind a salicylic acid and Covid-19 or Coronavirus is binding to lung and other tissues. The spike protein of Coronavirus binds to the cellular receptor ACE-2 now. As a physician, you've heard of ACE-2. This is the receptor that we associate with hypertension and the renin angiotensin aldosterone system. ACE-2 is expressed in vascular endothelial cells and renal tubular epithelium and the testes, and we know that from PCR, now that we're really studying this, we know that ACE-2 is also expressed in lung, kidney, and GI tract. Its typical ligand is angiotensin 2.

So the reason that our current antivirals don't work on Covid-19 is due to these spike proteins. The flu antivirals are antibodies that block the cyalic acid binding site of flu, but Covid-19 doesn't use this receptor. It's unlikely that those drugs are ever going to work for this virus. However, there are things that may work. There are ACE-2 antibodies that have been developed. They were developed actually for SARS and they've been shown to block viral entry in vitro. It's never been shown to block viral entry in a human yet. I was sent an article yesterday that suggests that chloroquine, which is a drug that we use for malaria, may also block binding. So there's hope there.

So here's where we are. We have this virus, we have the S protein, the spike protein, on the surface of the virus, but in order to get close enough to the cell to fuse with it, the virus actually has to cut off the receptors, and this is where Covid-19 is different than SARS and is different than MERS and is different than every other Coronavirus. Whereas the SARS virus didn't have

an easy way to cleave off those receptors, the Coronavirus that we're dealing with today has a furin cleavage site and most cells express furin. That allows the virus to get into them, even if they don't have a lot of ACE-2 on their surface, which means that this virus can even get into the CNS, CNS being central nervous system, brain.

I think that's really important for a clinician to understand because you may see clinical manifestations that you don't expect. We're hearing all about the upper respiratory manifestations, but there actually are patients with CNS manifestations and you need to be able to recognize those as well. So this is what's making this particular Coronavirus a thousand times more infectious than any other Coronavirus.

And then there's a second component of Covid-19 that makes it more deadly. And that happens once the virus gets inside the cell. Once it's inside the cell, now it stimulates something called the inflammasome. And this is from your own human cells. And inflammasome might be new to you if you haven't been studying immunology in the last 5 years. So the inflammasome is what we call the collection of proteins receptors and mediators involved in inflammation. We just term that inflammasome.

Activation of the inflammasome is what's causing uncontrolled inflammation, and we're observing this most in the lungs, but it can involve any tissue that gets infected. So there's 2 viral proteins involved in stimulating the inflammasome. These would be the virus' virulence factors, and if the virus doesn't have these 2 proteins, then it isn't pathogenic.

Importantly, these virulence factors are what's leading to what's called a cytokine storm, and there's been a lot of chatter on the internet about cytokine storms, so let's just clarify what a cytokine storm is. Usually cytokines are secreted in limited amounts, but sometimes pathogens can stimulate these cytokines to go out of control. In other words, the gene doesn't get turned off. In the case of Covid-19 one of the virulence proteins can trigger the overproduction of interleukin 1 beta. That's the cytokine storm we're seeing and it is a result of the virus, not of anything anyone is doing to treat the virus.

Gazella: That was a great explanation as to why this is more infectious and more deadly than the cold and flu. And I want to stay on the cold and flu just a tiny bit more.

Zwickey: Yeah.

Gazella: With the common cold and flu, it typically goes away when the weather gets warmer. Can we expect that to happen with Covid-19 or is that just wishful thinking?

Zwickey: Yeah, it's probably wishful thinking. So there's 3 primary reasons why viruses diminish in the summer. The first is vitamin D levels tend to be higher in the summer and lower in the winter. Sorry. Yeah, lower in the winter. So if your vitamin D levels increase, you tend to fight off viruses better. Secondly, people are often inside in the winter where there's recirculated related air and they're closer to each other so we get more viral spread.

Zwickey: And then finally, respiratory droplets tend to stay in the air longer in cold air. So you would think all of these things would be true for Covid-19 as well. However, if they were, we would expect to see a greatly reduced viral spread in warm climates. And while we are seeing lesser spread in Australia, we don't see lesser spread in Spain, and several African countries are now starting to see spread, so that suggests we're not going to see a seasonal effect with Covid-19.

Gazella: That's a great explanation. Now I want to get to some misconceptions or possible myths. The French government made a pretty significant claim recently that ibuprofen and NSAIDs can reduce a person's ability to fight the Covid-19 virus. That's caused some debate. What's your take on that?

Zwickey: There was an article yesterday in the *British Medical Journal* that suggested that ibuprofen can indeed exacerbate disease. And that goes back to the fact that this particular virus is targeting that ACE-2 receptor and the renin angiotensin aldosterone system. So that whole system is going to be dysregulated with active disease. Now, ibuprofen is a cox inhibitor and the cycle oxygenase enzymes are essential for renin release. So if you're taking a cox inhibitor, you're putting more stress on that whole system. And as a result, it's probably going to make disease worse. If you're taking acetaminophen, it doesn't have the same effect because it's not an NSAID, it's not a cox inhibitor. So I would just say switch to acetaminophen because there's additional things that are happening that we're just starting to discover right now. It's possible for example, that Covid-19 is downregulating aldosterone, which as again a part of that system and just not stressing the adrenal angiotensin aldosterone system is going to be important.

Gazella: Yeah, that's fascinating. So this is true, ibuprofen can in fact reduce a person's ability to fight Covid-19 so that is good information. Now another issue that I think needs to be clarified is risk. For example, with Covid-19 children don't seem to be at a high risk. Why is that? And who is considered high risk when it comes to Covid-19?

Zwickey: So there's so many things that can affect risk. We know, for example, that melatonin levels are inversely correlated with risk. And for example, kids have the highest melatonin levels and the lowest risk. So there's scientific plausibility to this argument because we also know that melatonin can decrease NF-kappa B and decrease the inflammasome and the inflammatory process. So those 2 things could go hand in hand.

There is absolutely no evidence at this point that administering exogenous melatonin is therapeutic. So even though there's a correlation, and these correlations are promising, we don't know that melatonin is therapeutic. And remember melatonin is going to put people to sleep. So be cautious if you're thinking that melatonin is going to be a therapy. And remember that other enzymes change with age. We see increasing inflammation with age and it's possible that it's actually the underlying inflammation that is putting people at greater risk. So other hormones and neurotransmitters could also be involved. We're really in the infancy of the research on this virus.

Gazella: So who is at risk? How do you describe that category? High risk, I should say.

Zwickey: So high risk is strongly correlated with age. We know that if we're looking at risk for death, that is, the older the person, the higher the likelihood of death. Risk for infection has to do with exposure, how many people you're being exposed to, right? And not, I don't want to say how many people who have Coronavirus because you don't know who has Coronavirus. There are a lot of people who are carriers who don't have any symptoms at all. So just exposure to people in general is putting people at risk.

The other thing that's causing risk is people who are immunocompromised who don't have an immune system strong enough to fight off this virus. So think about people who might have HIV, people who might be on chemotherapy or some other pharmaceutical regimen for COPD for example. We know that hypertension is a risk, again because of the system that's targeted by this virus. So hypertension and cardiovascular disease tends to be a very strong risk even if you're not old. And to me what's sobering about that is the number of people who are young, who have uncontrolled blood pressure because that means they are at risk.

Gazella: That's really good. And you mentioned immunocompromised, I've been trying to read about autoimmunity and I've read mixed reports on autoimmunity. Like if you have an autoimmune condition, are you at risk? What's your view on that?

Zwickey: It depends on the treatment that you're taking for your autoimmune disease. So if you have an autoimmune disease but you're not taking anything that suppresses your immune system, you're likely going to be fine. However, if you're on biologics or you're on something like methotrexate, your immune system is partially shut down. And so then you're going to be at a much higher risk.

Gazella: That's a great clear explanation. Thank you for that. So you mentioned people who don't have any symptoms and I think that's probably the most troubling aspect of the newer information that's coming out, asymptomatic or mildly symptomatic people can transmit the disease and they can spread it to large numbers. I think the average that I read was 3 to 5 people or something like that. So that goes back to why it's so infectious. Is that why social distancing is such a big part of the equation right now when it comes to controlling the spread?

Zwickey: Absolutely. We initially only thought that Covid-19 was deep in the lung, when it caused these lower respiratory infections and pneumonia. And the first time you and I talked, that was the information we had. Now, what we're seeing is that Covid-19 is actually also an upper respiratory system. So it can be carried in the throat in the upper respiratory system and you can spread it to others without showing any symptoms yourself.

Gazella: Yeah.

Zwickey: The folks who are doing that are vectors, right? They're spreading virus to people who may not be as healthy as they are. So just because you appear healthy, it doesn't mean that you aren't a carrier and aren't spreading disease to others.

Gazella: Exactly. And when dealing with patients who do have a strong immune system or are healthy still adhering to social distancing and other CDC rules is absolutely critical. Correct.

Zwickey: Absolutely. Yep.

Gazella: So now Dr Fauci has called the government's response regarding testing a failure. This might be an unfair question, but I'm going to ask it anyway. Where do we stand with testing? Do you know?

Zwickey: I wish I knew. I've seen some estimates that say there will be 2 million tests by the end of this week. What I don't know is whether that's enough. I know that the president announced today that he's putting testing in the state's hands, which is kind of an interesting thing. Usually you would have a federal testing for this sort of pandemic, but this is one way that different states can take control if the state has enough resources to do so.

Gazella: Yeah, it is kind of troubling, because he's also talking about ventilators at the state level and just a lot of pressure at the state level. So I've been kind of following that as well. Now let's switch gears a little bit and talk about the immune system in general because of course that is a big area of your expertise. Now our listeners are well aware that we can bolster the immune system to help defend against viruses. I want you to just remind us what part of the immune system we should focus on to shore up our defenses against viruses.

Zwickey: So we know that for the average immune response against a virus, you want a TH1 T cell response. This is going to stimulate your CDAT cells and your NKT cells to kill any virally infected cells. That's what you want upfront. And then you want your immune system to calm down. You want to stimulate T-regs to help you end the response once the infection is under control. For the folks who are really struggling with this virus, it sounds like their T-regs aren't as active. So the best thing anyone can do for their immune system of course, is to have a healthy gut because your healthy microbiome is going to increase the Tregs, which will be involved in reducing inflammation. And it will also help with those TH1 cells early in disease.

Gazella: Perfect. Now you've made it quite clear that there's absolutely no evidence that an herb or dietary supplement works against this particular virus, but let's talk a little bit about substances that may have been shown to work against other viruses. Now, what natural substances would you highlight when it comes to enhancing immunity, that type of immunity that you just mentioned from a preventive standpoint?

Zwickey: Yeah, there are a number of antiviral herbs and do we know that they work against this virus? We don't, but a lot of these herbs have been shown to be effective against other viruses and multiple viruses, so that means that there's some hope there, and those would include things like astragalus, echinacea, goldenseal, Oregon grape, elderberry, those are the herbs that have evidence to show that they are effective against multiple viruses. Vitamins are also important. When I think immune system, I'm thinking vitamins A and D and vitamin C for shutting down some of the reactive oxygen species.

The interesting thing with vitamin Cs that we know ascorbic acid, can reduce the specific inflammasome that's associated with this disease. So it actually might be very helpful. Sleep. Sleep is super important for having a healthy immune system. And as I said, melatonin seems to correlate with this particular virus. So making sure people have good sleeping hygiene is going

to be important. And of course, reducing stress. Yes, that's easier said than done, especially if you're following the story. But we know that IL-6 is associated with anxiety and catastrophizing and IL-6 is known to make this particular infection worse. So the more you can reduce stress, the better.

Gazella: No, that's good information. Now what about reducing severity, once a person has a viral infection, are their natural substances that could possibly help with that?

Zwickey: Yeah, so this is important because prevention and treatment are actually pretty different for this particular disease, especially if people have activated that particular inflammasome that's causing so much of the problem. So the particular inflammasome that is stimulated is called NLRP3 I know that's a mouthful. NLRP3, that means that any therapies that reduce NLRP3 could be effective. Melatonin and ascorbic acid have both been suggested, to reduce NLRP3 and indeed they do. There's evidence prior to this outbreak that they can reduce this particular inflammasome. Other things that we know that can reduce this particular inflammasome are rosmarinic acid, something rosemary, lemon balm, even cannabis, cannabis has rosmarinic acid. Reducing IL-6, also seems to be helpful based on data out of China. In fact, in China they developed a drug that reduces IL-6 and it's being tested right now in Italy.

So what can we do to reduce IL-6? Well, again, lower your stress levels and you can do that with a simple visualization. Like you could do this with your kids if they're nervous where you just have them close their eyes for 5 seconds and imagine something that they love like puppies and their IL-6 levels will go down, but we can also do it with herbs. Lemon balm, passionflower, and ashwagandha have all been shown to lower IL-6, as well as feverfew. In fact, that's why we think feverfew reduces fever is it lowers IL-6. Also, remember that this inflammasome is critical to being able to fight the virus. It's just that it doesn't get turned off, so you don't want to actually take the inflammasome to zero. You don't want to over do it on any of this stuff because otherwise you won't fight the virus at all. So you do want to reduce the inflammasome, you don't want to take it to zero.

Gazella: Okay, that makes a lot of sense. And before I asked the final question, just by way of disclosure, I want to confirm to our listeners that you have no connection to dietary supplement manufacturers in terms of getting income or just to do any disclosures. Do you have any disclosures to make to our listeners?

Zwickey: I do have a disclosure. I have a supplement company, but I'm not talking about any particular supplement today and I'm actually not going to encourage people to go out and buy supplements right away, especially if you don't know what you're doing. Like if you are monitoring inflammation with a physician, naturopathic or otherwise, then it's fine to try these things. All of this is experimental. We don't know what's going to work on this virus.

Gazella: Yeah, thank you for your balanced view. I really appreciate that and that's why I wanted to reach out to you to have you talk to about this today. Now as I said, I do have one final question and I think it might be the most difficult, but I'm going to have you try to speculate how long you feel this crisis will last. What can we expect to happen in the near term?

Zwickey: Yeah, it's a really great question, right? So if you look at the mathematical models, it looks like the U.S. Is just starting up the steep side of the asymptote, which means it's going to happen for a long time. We heard initially 2 weeks and then 4 weeks and now people are saying it can still be hanging around in July and August. I think what we're going to see is, I personally, what I think we're going to see is we're going to see our peak happening in around 3 weeks and then it'll start down the other side, but it's going to be a slow decrease. The other thing that I think is important is we keep looking at other countries for information and the U.S. is its own beast. It's different than other countries. For example, for this particular virus, I've already talked about the fact that it's binding to this ACE-2 protein, and what that means is that people who are on ACE-2 inhibitors are going to likely have a higher viral load because ACE inhibitors actually increase these receptors.

Well Americans have more people on ACE inhibitors than anywhere else in the world. So it's entirely possible that we're going to have a higher risk than other countries simply because of the medications that people in this country are taking. It also means that following the infection you could actually see heart damage as a result of the infection. Even if the infection resolves or you're one of those people who doesn't severely get the virus. So the ramifications of this virus are not going to be gone in 2 weeks. We're going to have still infectious disease around probably for a few months and we're going to also have the longterm effects to deal with, with a lot of people having some heart damage. The other thing to remember with Coronaviruses is that they often have a second peak in the fall and no one's talking about that right now. Nobody wants to think about that right now, but it is entirely possible that this is going to show up again in October. So we don't know, this is a different piece than other Coronaviruses but it's entirely possible.

Gazella: Yeah, well thanks for that information. Some good points about why we are different than other countries because we are really looking to other countries to try to trend this out and predict what's going to happen. So you bring up some great points. Now, Dr. Zwickey, this has been very informative. Thank you so much for sharing your expertise with us today.

Zwickey: You're welcome.

Gazella: So there has no doubt that this is a difficult time for this nation, patients, as well as the healthcare professionals who care for them are anxious during this time of social distancing. Let us not forget the powerful words of integrative health pioneer, Dr. Rachel Naomi Remen, who said, "When we know ourselves to be connected to all others, acting compassionately is simply the natural thing to do." Thank you for listening and please share this episode with patients, colleagues, friends, and families. We stand with you during this challenging time.

About the Author

Natural Medicine Journal is an electronic peer-reviewed journal and open access website dedicated to the field of integrative medicine.