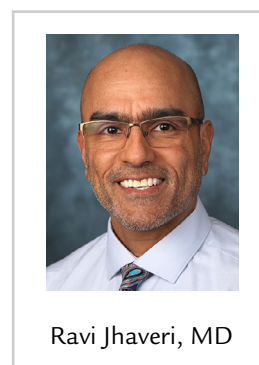
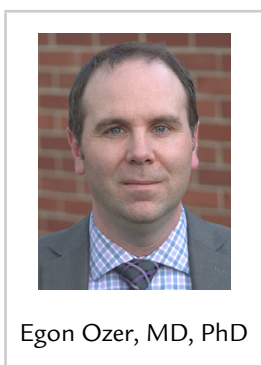




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Conversations With the Editors: The Emergence of Variants Amid Population-Wide SARS-CoV-2 Vaccination Efforts: How Much Should We Worry?



Feature Guest Biographies: Egon A. Ozer, MD, PhD is an assistant professor of medicine in the Division of Infectious Diseases at Northwestern Memorial Hospital and the director of the Center for Pathogen Genomics and Microbial Evolution in the Northwestern University Feinberg School of Medicine's Institute for Global Health. His research focuses on whole-genome sequencing and comparative genomics in microbial pathogens to answer questions about epidemiology, transmission, virulence, and antimicrobial resistance. Larry Kociolek, MD, MSCI, is an attending physician in the Division of Infectious Diseases and Medical Director of Infection Prevention and Control at the Ann & Robert H. Lurie Children's Hospital of Chicago, where he is the institutional lead for COVID-19 response efforts. He is an assistant professor of pediatrics at Northwestern University Feinberg School of Medicine. Dr Kociolek's research efforts are focused on clinical and molecular epidemiology and prevention of health care associated infections and infections caused by high-consequence and emerging pathogens, particularly *Clostridium difficile* infection and SARS-CoV-2.

EDITOR'S NOTE

During the last several months, significant attention has been devoted to the emergence of variants of SARS-CoV-2. These media reports often describe how the *variant du jour* is now the most common one seen in a community or country, and the tone is one of alarm. We wanted to provide the proper context for our *Clinical Therapeutics* readers because there is quite a bit of good news to counter these reports. I sat down with 2 experts in the field of molecular epidemiology and infectious diseases, Drs Egon Ozer and Larry Kociolek, to discuss these issues.

Dr Jhaveri: Okay, thanks to both of you for joining us. We really appreciate your time and expertise. Dr Ozer, maybe we can start with you. As level setting for our readers who may be less familiar, could you offer a brief explanation of what we mean when we talk about SARS-CoV-2 variants? And then because of your research interests, could you review for us sort of the evolution of variants that have emerged during the pandemic?

Dr Ozer: Sure, I'll try to keep it brief as there's a lot I could say about variants. We'll start off by saying that as far as SARS-CoV-2 mutating, it is not unusual. It's what it's supposed to do; the source genetic code of the virus is changing every time it causes an infection.

There's a potential to make little errors or mistakes in its genetic code that sometimes will be detrimental, to make it less fit to cause infection. Sometimes the changes will be completely neutral. Sometimes we will see that mutations provide some sort of advantage to the virus; then we might see those propagating on and spreading to more people. That's generally how these variants tend to emerge. So, what we know is that since the very beginning of the COVID-19 pandemic, there has been emergence of new lineages and new variants that have caused infections. The earliest that we know about was way back in February or March of 2020; there was the acquisition of a mutation within the Spike protein (one of the most important for the virus to bind and then be taken up by the human cells to cause infection), and we know that there was a mutation there that resulted in the virus being able to stabilize the spike protein to become more efficient at causing infections of human cells. That mutation then propagated and spread around the world and crowded out some of the other versions of the virus that we'd first seen in late 2019 and early 2020.¹

Since that time, mutations have continued to occur, and some of these newer variants are what you hear about in the news or in the literature. Some of those are specifically ones that are concerning to us as physicians and public health experts and scientists because they are ones that seem to be associated with some advantage, whether that's increased transmissibility or more severe disease or worse outcomes in disease. These are all things that we are concerned about with some of these newer and emerging variants.

Dr Jhaveri: All right, thanks. Dr Kociolek, we're going to switch over to you. Can you talk a little bit about what information we have about how these emergent variants have been linked with either surges in cases across the globe or more severe outbreaks? I think the debate for a lot of the readers is does the outbreak come first and then the variant emerge or does the variant emerge to cause the outbreak?

Dr Kociolek: I think those aren't necessarily mutually exclusive concepts, and I think sorting through these things is extraordinarily difficult in a real-world situation when you're outside of a laboratory. For example, the concept of transmissibility depends on the pathogen and how efficiently it can spread between people, but it also depends on the behavior of individuals who are susceptible to infection and measures taken to prevent additional exposure and infections. We know Ebola, for example, is exceedingly transmissible, but if the cases are rare, we can identify them quickly and isolate, and then transmission is exceedingly unlikely. So, when we're comparing these variants that are emerging worldwide in the setting of gradually relaxing risk mitigation measures, such as less masking and social distancing, the human behavior element is much, much different.

What we've seen in Chicago is that the variants, meaning the alpha and the gamma variant, which are most prevalent in the United States right now, started to emerge in Chicago around the same time the vaccine became available in late December. Despite the proportion of variants increasing significantly, the case counts declined, showing the vaccines were effective. We saw a small increase in cases in the spring that seemed to be more related to spring break travels, again highlighting the changes in human behavior that impact transmissibility. Since that time, cases have declined dramatically, despite nearly every case in the Chicago area being related to a variant of concern or a variant of interest.

Certainly, what they've seen in other settings where this has been looked at in a more appropriate experimental setting is that these variants do have the ability to transmit between people more effectively. However, there's no doubt that risk mitigation, such as masking and vaccines, remain extraordinarily effective at preventing transmission irrespective of which variant we see.^{2,3} The concern with the ongoing evolution of the virus is whether there will eventually be a variant that emerges that is no longer vaccine preventable or can cause more severe illness. Those things have not yet been seen for any of the variants.

Dr Jhaveri: Before we get to vaccine, I just want to follow up on one point that you made, and this is really for either of you. Looking at current cases now and the idea that the vast majority of them, whether it's the delta variant emerging as the primary isolate across the rest of the country, are in the unimmunized population. The question is, given how transmissible SARS-CoV-2 is, would these people ultimately have been infected, regardless of which

variant we're talking about? It's a question of sooner versus later, and the bottom line is that the virus is finding the susceptible host versus whether it's a variant or not.

Dr Ozer: I can address that. I think both things are true. I think that potentially those who are unvaccinated or undervaccinated, they may have been, you know, having lifestyle choices or decisions that may have made them more prone to have more exposures and eventually got an infection. That being said, the variants are different, especially the delta variant and the alpha variant. What we know about them is that the alpha variant is at least 50% more transmissible than lineages that came before it. The delta variant is 50% more transmissible than the alpha variant, which is about 75% more transmissible than the earlier lineages that were circulating through most of last year.⁴ What it comes down to is that some of the mitigation measures that people were taking previously may not have completely gone with the perfect recommendations in terms of always wearing a mask, always making sure that you're 6 ft apart, being in smaller groups, and limiting their time with other people. Those things might not be as protective now with some of these newer variants as they were previously. The risk is just that much higher that even with a smaller dose of infective material, so there is still an increased danger and that people that might not have necessarily gotten an infection previously are at a higher risk now.

Dr Kociolek: I agree with everything that Dr Ozer said. We saw superspreader events immediately (in the pandemic), right: that big technology conference in Massachusetts, the cruise ship experience. We know that the wild-type version of this virus was able to cause large superspreader events. Nothing's changed with that potential. Now, with these 2 variants, the alpha and delta in particular, that are more transmissible, the potential for those superspreader events increases among large group gatherings. So, while I don't think the emergence of variants necessarily is forcing us to change paths or to reconsider our risk mitigation strategies, it's reinforcing the need for those risk mitigation strategies, particularly vaccination.

With an increasingly vaccinated population, the fact is that there is still moderate- to even high-level transmission in some communities throughout the United States that seems to be associated with lower vaccine rates.⁵ Ultimately, for those who are not vaccinated, the likelihood of them getting infected, particularly in those communities, is going to increase over time with more transmissible variants.

Dr Jhaveri: Now that we're talking about vaccine, can you share with us what is known about how vaccine protects against these emergent variants?

Dr Ozer: What we know is that the vaccines that are available in the United States currently, which are the 2 messenger RNA (mRNA) vaccines, produced by Pfizer and Moderna, as well as the Johnson & Johnson single-dose vaccine, we know that they're highly effective against all the variants that have been tested and that are currently most predominant in the United States and around the world.³ We know that there's been some decrease in efficacy of the vaccines against some of these newer variants, especially the delta variant. We see a slight decrease in the effectiveness of the Pfizer vaccine against these, but it seems to be clinically not so significant. We know that it's sort of a drop for those who are fully vaccinated from the low 90% efficacy to about 88%. In real-world terms that doesn't seem to make much of a difference. We know there's still a very high degree of protection against severe disease and a very high degree of protection against death from COVID-19 in people who have been vaccinated. We know that in the month of May, recent studies suggested that more than 98% of those who were hospitalized with COVID-19 infection were unvaccinated or undervaccinated. For those who died, more than 99% were unvaccinated or undervaccinated, so we know that the vaccines are highly effective.⁵ If there is any sort of marginal fractional decreases in their effectiveness against some of the newer variants that we know about right now, the protection against severe disease and death is still very, very high.

Dr Kociolek: I would add on to that there is a difference between in vitro immunological assays and clinical immunology. You will find studies that show significant and sometimes alarming differences in neutralizing ability with in vitro assays, but those differences in neutralizing ability are not translating into substantial differences in

clinical protection against these variants.⁶ So, it's very important as we understand the terminology around variants that we're really focusing on population-level vaccine effectiveness. I would add that the effectiveness of vaccines, irrespective of whether or not it's a variant, may impact durability of the vaccine. We've only known about this pathogen for a year and a half; we've only known about vaccines for 6 months. We don't have longitudinal data yet, but at least modeling studies have suggested that vaccines that start with a much higher level of effectiveness, such as the mRNA vaccines, may give much more durable protection. It's estimated that mRNA vaccines could provide several years of protection against severe disease. The last thing I'd like to point out is that when we close this chapter in global public health, I think we're going to recognize the emergence of mRNA vaccines as one of the most substantial public health accomplishments in my infectious diseases career to date. One of the benefits of those vaccines is that the technology was developed to respond to emerging threats because they can be modified quickly. Moderna and Pfizer already are looking at boosters or multivalent vaccines that can include variant spike protein mRNA, and so I think we have the tools in place to be able to rapidly respond to this, as long as we have good molecular epidemiologic surveillance, good clinical surveillance, good public health measures, and strong scientific and clinical trial systems. I think we have the tools in place to respond to this.

Dr Jhaveri: Thanks to both of you. I just would add for the readers that it's really important when we discuss all these numbers around vaccine effectiveness that we highlight what they really mean. Just because you're infected, that doesn't necessarily mean that you're going to have any clinical symptoms at all. Highlighting what Dr Ozer mentioned that people who are vaccinated are highly protected against clinical symptoms of any kind, and certainly from dying or being hospitalized, which is what we really are aiming to prevent.

Dr Ozer: The other number worth keeping in mind, and it's one that's a little harder for us to know right now, is your potential for transmitting to others who are unvaccinated. Even if you're in one of these age groups that used to think that your likelihood of severe disease is going to be lower and so vaccine may not be as important for you, you have to keep in mind that every infection has potential to transmit to somebody who might not necessarily have the same protections or who might not respond as well to the vaccine. That's the other external factor to keep in mind with vaccines: it is not just what is going to happen to you, but what is going to happen to the people around you if you are or are not vaccinated.

Dr Jhaveri: Excellent points. Thanks for adding them. To bring us to a close here, let's talk a little bit about our public health strategies going forward. The public obviously heard a lot of concern in the news and from public health authorities about the emergence of variants, so they're understandably a little bit panicked about what to do. How should we be advising them, and how should we proceed in terms of our public health measures?

Dr Ozer: I'll start and let Dr Kociolek add on to that. I think that there's a lot of alarmism about variants, and it can dilute the message. Every time a new variant emerges, which I already said is what's going to continue to happen and is not unusual or unexpected, there's new stories about how deadly and how dangerous it is. Every time that happens, I think there's less and less of a response to it, and every time the world doesn't end when a variant emerges, then you know it doesn't seem a whole lot different. I think that can make it difficult on the public to understand what the point is and whether these things are really as bad as everybody says they are. Just because it's not the second coming of the worst plague, these variants are incrementally sort of more dangerous each time. It may not translate into a huge outbreak, but every time that this happens there's potential for a little bit of an increase in transmission and more cases, and there is potential for a little bit of a decrease in the effectiveness of the vaccine and so more infections that can happen from that. These variants should be taken in the context of every time as an indication that we really need to double down on the public health interventions that we're doing, including vaccination, social distancing, masking when necessary and in the right context. What we want to do is break the cycle, we want there to be fewer emergences of these variants, we want them to occur less frequently, and we want them to be less dangerous when they do emerge. I would just counsel the public to step back and look

at it in the context from the beginning. As we're seeing variants emerging, that's an indication that we need to be doubling down and getting better control of the virus.

Dr Kociolek: The variants present the potential for a spiraling public health crisis, but everything we know right now is that we have the tools in place to keep everyone safe if those tools are utilized. With pockets of high community transmission associated with high proportions of variants and low vaccine rates, those adults who are filling intensive care units that are running out of ventilators are predominantly individuals who are not vaccinated against SARS-CoV-2.

These variants are not requiring us to reinvent the wheel. We need to just not be comfortable with our 50% to 60% vaccine rate in the United States and keep pushing that to keep everyone safe and to get our country and social systems back on track.

Dr Jhaveri: Thanks to both of you. I would just perhaps add that we also need to bolster our global vaccine strategy and every global outbreak presents us with the risk of a new variant emerging and then being transmitted to the United States and finding those pockets that are unvaccinated. As much as we push our local efforts for vaccine and vaccination, I think we also need to keep in mind that this is a *one-world* strategy, and we need to bolster our colleagues and other countries as well.

Dr Ozer: Absolutely. The virus does not respect country borders, so it needs to be a global strategy, I totally agree with that.

Dr Jhaveri: Before we close, any last comments you guys would like to make?

Dr Kociolek: I would just like to point out that the one silver lining to what we've learned about variants is the national and local health department investment in molecular epidemiologic surveillance, which has always been a critical missing piece from our study of infectious diseases. That's something that I think we'll be able to build on, that will improve surveillance efforts for epidemic and endemic infections for years to come.

Dr Ozer: I think you took the words out of my mouth. I think the molecular epidemiology, the molecular genetics, and genomics of studying pathogens is a very important part of not just this pandemic but preventing the next one and even dealing with the ongoing pandemics of things like antibiotic resistance. Those things have not gone away and they're continuing, and genetic surveillance is going to be a very important tool. I think it's been highlighted over the last year and a half just how important it is.

Dr Jhaveri: On behalf of our *Clinical Therapeutics* readers, I want to thank both of you for your time and for sharing your expertise. We appreciate all the work that you're doing, both in the setting of the pandemic and throughout the field of infectious diseases. Thanks so much.

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