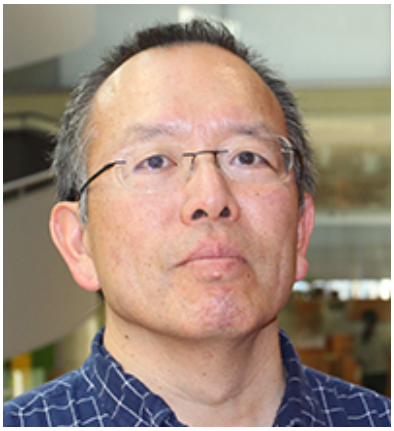
COVID Information Commons (CIC) Research Lightning Talk

Transcript of a Presentation by John Yin (University of Wisconsin, Madison) September 23, 2024



Title: Ecological Dynamics of Human Coronavirus

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Transcript

Slide 1
Great, thanks a lot to the COVID Information Commons for building the community. I'm happy to have an opportunity to share a little bit of our interests. I think of this as a broad community that includes not only data scientists, but social scientists. I've tried to put together a talk that will be understandable by all. The title has changed a little bit, so rather than Ecological Dynamics, I will focus on Evolutionary Dynamics of Human Coronaviruses and what one might be able to learn from such processes - they might actually inform how we think about new strategies for preventing future pandemics, as COVID-19 persists.

Slide 2
This is a bit out of date, but this is from August 2024, last month, where there have been over 7 million deaths globally. At that time, there was some increase over the previous seven days. People continue to be infected and the cases, at least in August (last month), were increasing over the last 28 days or so. The numbers are certainly much lower than they were at the height of the pandemic, but we know people are still getting infected. We don't know what will happen in the coming months or years. Why does it persist?

Slide 3
Well, basically the virus SARS-CoV-2 continues to evolve. I won't go into the details - this was nicely reviewed last year. Essentially, if you look at this figure from a timeline - from January

2020 to December 2022, you see a bunch of different colors appearing and disappearing. These are correlated with various strains of the virus isolated from patients over this period. Essentially, the virus is being displaced and various strains are being displaced by new strains that are continuing to evolve. So it persists because it evolves and we know that. We have each hopefully gotten vaccinated at least once, and in many cases, multiple times, to protect ourselves.

Slide 4
And we're being protected against current or past strains, not necessarily future strains. Likewise, there are drugs that have been developed to target specific virus functions as well as antibody types of therapies. Again, however, these are targeting viruses as they've existed in the Lab and we have seen resistant viruses. To better understand what's going on in these systems, I thought I'd go back to some basic virology.

Slide 5
I'll share a famous quote from some immunologists: "A virus is simply a piece of bad news wrapped up in protein." The bad news is the genome shown here, schematically, as this linear entity with various genes. That's the genome for SARS-CoV-2, the virus that caused the pandemic. When we say it's wrapped up in protein and this genome is put into a nanoparticle and the surface of this particle, the various spike proteins that the virus uses to enter cells.

Slide 6
This particle then, when it encounters a susceptible cell, whether it's in the brain or in the respiratory tract, sends the bad news into the cell. That bad news gets amplified into something we might call "followers" for the biologist. These are messages from the virus and proteins. The "followers" of this bad news amplify the bad news, make more of it. They also package the bad news and make new virus particles, which are then released into the external world of the cell. They can go and infect other cells. The news is bad because, generally, the cell that receives the bad news dies in this process of transforming a single virus into anywhere from 10 to 10,000 virus particles. This is how bad news spreads. A byproduct of this process that is not widely appreciated is that the bad news can also make what we would call "fake news."

Slide 7
In addition to amplifying the bad news during a normal infection, a byproduct of this process is to make genomes that are defective, lacking essential information needed for replication. We call these genomes defective virus genomes, or in this case, "fake news." They can also be packed into particles. We call them "zombie virus particles." In this case, a "zombie virus particle" is a piece of fake news wrapped up in protein. It's a byproduct of normal virus infection. Such particles have been known for over 50 years for virtually every virus, including coronaviruses, influenza viruses, adenoviruses, the list goes on and on .

Why do we call them zombie viruses? Well, we know zombies are dead, and this is no exception. The zombie virus, when it encounters a cell, can release its “fake news” genome into the cell, but because it is lacking essential information for growth, it fails to turn the cell into a virus factor. In general, the cell will not die. This is the end of the line for the zombie virus because I’ve chosen the term “zombie virus,” which you will not find in the broader literature, other than a Scientific American perspective article that I wrote a couple of years ago. Zombies, as we know, can spring to life, and this virus can spring to life under special conditions. That’s in the case that the zombie virus encounters a cell that is infected by an intact virus. The intact virus goes about its normal process of introducing the bad news, amplifying the bad news, making the followers, but if the fake news is introduced by the zombie virus, the fake news can divert the resources of the normal virus infection towards its own amplification. The fake news can get amplified, likewise, if it retains the signals that say “hey package me!” - then the fake news can be packaged into zombie virus particles. What happens is that one can get zombie virus reproducing at the expense of a normal virus. Again, this has been known for many viruses for many years. If you look at this figure and you forget about the zombie viruses, just look at the intact virus, you’ll notice that one virus goes in and maybe a smaller number of intact viruses are produced. This is exactly the sort of behavior we would like to have for antiviral therapeutics that reduce or inhibit normal virus growth. This idea has inspired many to ask if we could create zombie viruses that are therapeutic. A number of groups have done that - these are not my own group, but zombie viruses have inspired the engineering of therapeutic-interfering particles, virus-like particles that can divert resources from the virus towards their own replication. Those are a couple of prominent papers from a couple of years ago.

Slide 8

I’d like to return to the zombie viruses, but I also want to show a special case where people were looking at SARS-CoV-2’s evolution in Germany. What I show here is a single patient at the center. I’m not sure if you are able to see my pointer? Ok, so here’s one patient who was in Freiburg, Germany, who was infected with SARS-CoV-2. We had a swab sample. This is from the paper that they published - they swabbed the person and they got the genetic sequence. They then tracked other people who were infected in Freiburg. Each one of these other dots represents another person in Freiburg who was infected by a virus related to the initial one. Based on their swab samples and the sequence analyses, one can create this trajectory of evolution. Each of these individual dots are swab sample sequences showing that the further away you go from the center, the more evolutionary diversity, genetic diversity you have from these viruses. This is showing the evolution of the virus in Freiburg, Germany during the early pandemic in 2020 or so. Each one of these dots is a single patient, a single swab sample.

Slide 9

What I’m showing now is an additional evolution beyond that individual - there were additional swab samples taken. In the red box, they are radiating outward to indicate more evolution.

What's unusual about this is that this was from a single person, someone was immunocompromised. If you're getting an organ transplant, you'll receive drugs to treat and downregulate or inhibit your immune response so you don't reject the organ. If you're HIV positive, then your T Cells (which we heard about in the first talk) are going to be compromised - they will be less able to fight the infection. You might be actually sick for several months or even a year with your virus infection. This individual was sick for 120 to 140 days. Swab samples from this single individual indicated that the virus was evolving. It's hypothesized that such immunosuppressed individuals are sources for the genetic diversity that we see as the coronavirus evolves.

Slide 10

When we saw this, we spent a number of years looking at defective virus genomes and we wondered whether or not they might actually be present in COVID patients, particularly in the immunocompromised patients. This immunocompromised patient from the published work - from days 0 to 140 - the X axis represents time from early to late days and the Y axis are various virus variants. The higher the level they are, the darker the color. There are a number of columns here, 8 or so columns, where the strain that was present at day 0 persisted all the way through. These are the vertical columns here, but you also see indications where new dots appear and disappear or persist over time. These represent genetic variants of the SARS-CoV-2 virus. They are evolving in this particular patient. We went into the database with this particular patient and looked specifically for signs that there could be some zombie viruses - defective virus genomes that delete large sections of information.

Slide 11

This is the work of my Ph.D. student, Nan Jing, who needed to learn informatics from a collaborator, Colin Dewey. Eventually, she was able to create an analogous plot. Here's day 0 through day 140. Here are also various changes that are occurring and the X axis represents various deletions that are appearing, disappearing, or persisting over the course of this immunocompromised patient's infection. We don't know what this means yet, other than there's something that seems to be tagging along with the normal virus. There's evidence of zombie-like viruses and they might be co-evolving. One perspective might be that if you test positive for COVID, your symptoms can range from asymptomatic or not severe all the way to critical.

Slide 12

Another perspective might be that if zombie viruses are prevalent at higher concentrations, they're inhibiting the normal virus and you're having a less severe disease, whereas if you are testing positive, you have very little zombie virus. Perhaps they're not inhibiting the virus very well and you're getting a more critical severity of disease. This is one hypothesis.

Slide 13
We've also looked at other immunocompromised patients who are under surveillance. We've looked at their zombie virus and defective virus genome frequencies. We've seen in some cases, patients who recover have lower frequencies. In one case, a patient who died from the United Kingdom and was immunocompromised - they had higher levels of the defective virus genome. This shows that it's possible that they could perhaps be not protected, but correlated with more severe disease. We don't know what this really means, but it opens up a number of questions. One is: how are virus-like genomes or defective virus genomes, how are the zombie viruses linked to disease severity?

Slide 14
We've suggested that they could be causing more or less severity. We'd like to better understand how these defective virus genomes or zombie viruses function. How do they interact with the resources of the normal infected cell? During co-infections, how do they activate immune responses, either innate or adaptive immune responses? Ultimately, are there design rules that we could figure out from studying these beneficial defective virus genomes?

Slide 15
I've hinted towards the idea that they might be helping us prevent future pandemics. We have drugs and vaccines that interfere with normal virus growth and activate protective immune responses. A claim here is that these therapeutic interfering particles can do the same, but they also offer additional possibilities. One is that they amplify by preying on infected cells. Currently, there are no drugs or vaccines that amplify themselves in the presence of the disease. That's a potentially interesting feature of therapeutic interfering particles since they are virus-like and can transmit between hosts like viruses do. Current drugs and vaccines do not transmit between hosts. If you're an anti-vaxxer, it's conceivable that you could receive protection from someone who has been inoculated with a therapeutic interfering particle. Therapeutic interfering particles may also resist viruses because they create genetic variation that can allow them to resist the effects of drugs. Therapeutic interfering particles use the same error-prone machinery that the virus uses, so they have the possibility of co-evolving with the virus. There is actually work - very old work - that we are reproducing in which therapeutic interfering particles and viruses can co-evolve. If we think about the powerful new features of therapeutic interfering particles, we have to also recognize that there will be new risks. This opens up new ethical questions and it's important for us to be aware of these issues.

Slide 16
I have a number of great collaborators that I want to highlight here. In particular, Colin Dewey from Biostatistics and Medical Informatics who has played a central role in helping my graduate student come up to speed on bioinformatics. We also have people in the medical school and people working with immunocompromised hamsters, evolutionary biologists who are helping us.

That concludes my talk, thank you for the opportunity. Feel free to take a look at our website or contact me if I’m not able to get to your questions during today’s session. Thanks a lot!