

Virologist Dr. Stephen Griffin speaks on the COVID pandemic and the Omicron variant: Part 2

Benjamin Mateus
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This is the second of a two-part interview with virologist Dr. Stephen Griffin. Part 1 can be read here.

Dr. Griffin is an associate professor at the University of Leeds and the previous chair of the Virus Division of the Microbiology Society in the UK. He received his Ph.D. from the University of Cambridge's Department of Medicine at Addenbrooke's Hospital. He moved to Leeds in 2001, conducting post-doctorate research on the hepatitis C virus. Dr. Griffin was tenured in 2014 as an Associate Professor of Viral Oncology in the School of Medicine.

His academic interests include work on viruses, both as a cause and a potential cure for human diseases. Specifically, his work has focused on understanding and exploiting membrane proteins called ion channels encoded by viruses, identifying the mechanisms used by viruses to induce cancers in the liver and brain, and developing viruses as immunotherapies to treat human cancers.

He is currently a member of the Independent Scientific Advisory Group for Emergencies (Independent SAGE) and has been active in various government committees during the COVID-19 crisis. He has also been actively communicating through his social media and various public platforms on the science of the pandemic.

Benjamin Mateus (BM): Perhaps you can speak on Omicron, the BA.2 variant, and the mutations it harbors. I raise the question not necessarily from an explanation of the inherent inborn error in its genetic proofreading mechanism that leads to a mutation in its gene sequences every two weeks. After two years and billions of people later, it has gained tremendous ability to infect and partially evade immunity. How do these characteristics evolve?

Stephen Griffin (SG): People get a bit confused about this because people say that coronaviruses don't mutate as fast as influenza or HIV or Hep C virus.

I'd say that the establishment of mutations in a viral population has to do with two processes. One is the random events that take place. Like you say, it's a random change in the genome and they can either be beneficial or neutral or indeed harmful to that virus. And then that depends on the nature of that change ... whether it is a change in an amino acid of a protein that's important or disrupts a structural element of the RNA, all that sort of thing.

All those changes are random.

And the technicalities of it are that coronaviruses do try and slow that [mutation] process down. They have what's known as a proofreading mechanism in the way their genomes become replicated, which checks back to see if the replication machinery is making mistakes [and corrects them], and that is important for two reasons.

One, the rate of changes is slightly slower, but two, it also means that certain antiviral drugs that we would otherwise use against this virus

aren't usable.

The second aspect though, is whether that change becomes embedded. And for that change to become embedded, it needs to be beneficial to that virus or not make a difference. It's about the change in the context of the environment.

When the Wuhan strain of the virus first came out, we were completely immunologically naive to that virus. We didn't have antibodies that would prevent the virus binding to our cells. We didn't have antibodies against that spike protein.

So, what happens is across the world, a huge, say billions of infection events happening, you get that random change mechanism going on and from time to time something will happen that leads to a change predominantly in the spike protein, which is the attachment factor that the virus uses to get into the cell.

But not always. There are other factors involved as well.

But it will find that change that might mean it can bind to the cells better. It binds to the ACE2 protein better. Or, perhaps it is more efficiently cleaved into its active form, which happens because of cellular proteases, which cleave that protein. Or, perhaps it can avoid some of the newly established antibodies that we are making against it either because of infection or more recently because of vaccines.

Because of that ... and it's not that the new variant then goes out and stomps on the other viruses that are around. It's a simple numbers game. If that virus becomes more successful, then you're going to see more infections with that virus in that environment. And it will just start literally to out compete in the same way that gray squirrels out-competed red squirrels and different types of lady birds have out-competed indigenous lady birds in the UK. It's literally a competition. It's a natural selection event.

Now. That's not just one change. It happens slowly. It happens gradually over time, because these variants of concern are distinct lineages of the virus. They've been evolving for quite some time. And that's because they've accumulated dozens and dozens of changes for Omicron compared to the original ancestral virus that we saw two years ago. The virus is doing this, and it does it in all sorts of different directions and all sorts of random paths, but predominantly you find something that's beneficial and add to it in different branches.

Okay. So, for example the variants that we term Delta and Alpha evolved in a certain direction that made them more highly transmissible. It made that binding interaction more powerful. It made the processing of the spike protein more efficient. And for that reason, although Delta did also have properties that evaded antibodies to some extent, Alpha was mainly increased transmission.

Omicron, HIV and Africa

Omicron, and other variants that people may have heard of like the Beta and Gamma variants, which were in South Africa and South America previously, they were much better at avoiding those antibody changes. There are other changes in the virus genome as well, but we're mainly concerned with the spike protein at present because that's the thing that's dictating transmission. And that's the thing that all vaccines are targeting.

Over time, if we take Omicron as an example, because it's really an extreme example because it has diversified along a different trajectory compared to some of the others, it's accumulated many more mutations. And to do that a virus has to have time and it also must have the right conditions.

So, the theory is that it probably happened in either a small population or a group of individuals who perhaps didn't have the most fantastic immune response. So that could be people that have HIV, for example. And the fact that's in sub-Saharan Africa is an element there because HIV is very prominent in that region of the world.

And so literally the virus is there trying out the different combinations over time. It may have been changing in someone that didn't have a very good immune system, trying to infect others, but not being successful. Then eventually it hits upon a combination of changes that give you Omicron.

It's incredibly successful. It's incredibly contagious. It is incredibly quick and able to replicate and pass between people. It's faster. It transmits more readily, and it evades our immune systems. There's one small blessing in that it seems to primarily infect our upper respiratory tract rather than our lower respiratory tract, but then most respiratory viruses that go into humans start to do that.

Highly pathogenic flu strains, like some of the H5N1 avian viruses, start low down, but most influenza that has eventually become endemic in humans has shifted up, again because of a change in the surface protein known as haemagglutinin. That doesn't mean that's going to be the case for the next variant.

There's a subtext to this as well because Omicron isn't just one lineage. It's three that we know of. There is the thing called BA.1 which swept around the globe recently before Christmas. There is something called BA.3, which didn't really take off. It's still there in South Africa, thankfully in small numbers. And then there's this one called BA.2, which has a great degree of overlap with BA.1, but not a complete overlap in terms of the changes that have occurred.

And it probably split from BA.1 several months prior to it escaping from South Africa. It has changes in different parts of the spike protein, and it has different mutations as well. It remains unclear yet exactly what the impact of BA.2 will be. But what is clear is that we are seeing an increase in its ability to transmit compared to the original BA.1 and some evidence that it's causing lots of reinfections even among people that were previously infected with BA.1.

However, we do know that recent vaccination, as was the case with BA.1, offers good protection, but it remains to be seen what impact BA.2 might have. But I think the major story from all this is that the situation with SARS-CoV-2 is not stable. It's still evolving. It's still changing and we're still not anywhere near any kind of steady state in terms of our immunity to it or all the viral evolution.

For that reason, the complacency inherent to just saying we're going to leave it with our vaccines and carry on as normal is a profound mistake because we'll start to count that cost. We're already seeing now an increase in infections in people over 55 in the UK again.

And that's translating to, whilst cases are still coming down on the downturn of the Omicron peak, it's going up in different age groups and down in different places across the country. We're starting to see more

hospitalizations and severe disease, which suggests that more vulnerable people are again becoming susceptible to infection. You guys in the United States have had a terrible time with Omicron.

So, people calling that virus mild are making a profound mistake because the clinical impact of a virus has to do with many things. But it's to do with the chance that an individual infected will become unwell, which of course is determined by their vaccination status or prior immunity, their resilience, their age and other factors.

But even if the chance of that [severe clinical impact] happening again, as with the ancestral SARS-CoV-2 variant which was very high, it's not as high it seems in Omicron. But you're only talking about a 50 percent reduction pretty much, but it infects so many more people. And again, it comes down to a numbers game.

You're seeing profound clinical impact in people that haven't got the correct protection against Omicron. And in the United States, you had a bad wave there. And in other countries too. We're starting to see BA.2 in places like Denmark, Israel, and it's becoming dominant in the UK now. It remains to be seen what will happen with that...

I think the UK is an unusual circumstance because we have had such a widespread vaccination policy that it may take some time before we start to see the full impact of this. But it says to me, that people saying the pandemic is over and talking about it in the past tense, that's incorrect.

BM: I'd like to ask a couple of quick questions along this line and then we can shift topics. Are we at a point that we can predict what these mutations mean or can do? And secondly, regarding the BA.2 wave in Hong Kong which is causing a profound health crisis: All the sequenced viruses harbor the I1221T mutation on the spike protein. Thoughts?

SG: In Hong Kong, I think it's two things. First, we don't know what the impact of that change [on the spike protein] is, but it's clearly there.

But I think Hong Kong hasn't had the best uptake in vaccinations by older people and that is the real problem, [though I'm not certain if this is correct or not]. There's been some vaccine hesitancy there which really is now causing them profound problems now that infections have gone out of control.

Going back to the actual individual mutations, these mutations can certainly have impact, and some have more impact than others. But it's always in the context of the other changes that are present. Because sometimes the change will happen that's just tolerated in something like Omicron and the actual effects of that won't be clear until we see it in much more widespread infections. So, in terms of guessing what a change does we can make good guesses now. But you can't completely say that you've got the real story until you've done full experiments in infectious culture.

Right now, we don't know enough about BA.2 yet. We're still only finding out about BA.1. I will really be interested to see what the entry pathway is for BA.2. I'll be really interested to see what the efficiency of the spike cleavage is, that pre-processing step that allows it to either engage more with surface ACE2 or go in through other pathways.

I think those are the sorts of things we need to see in addition to antibody evasion data before we understand what's going on. But it certainly seems again that if you've not been recently vaccinated, then your antibody defenses against BA.2 are struggling to prevent infection.

It's important to remember though, that if you have been vaccinated, a reinfection is generally not as bad, but not always. I think it's really important to understand that if you have huge numbers of infections, even that small proportion of people that will carry on having another severe episode means that you're going to have a huge problem with clinically vulnerable people who are still being overlooked, certainly in the UK.

This virus is not done. And we need to make sure that we're reacting to the changes that this virus shows us. You may have heard of the Delta-Cron recombinant that's been identified. We can't say for sure that's going to have the combined properties of Delta and Omicron until we

understand how those things interact in the context of the new virus. It's not right to panic, but it's certainly right to keep an eye on these things.

And I really worry that our downscaling of testing and surveillance, lack of border controls and lack of mitigations is going to mean that by the time we see something that hits us hard again, we're going to be so far behind the curve that it will be even more harsh restrictions necessary to get back in control. This is the irony of the sort of approach that yo-yos between lockdowns and freedom. I think a sensible level of mitigation is much better because ideally, we'd never end up having to lock down again.

Long COVID and other post-viral syndromes

BM: Post-viral syndromes, Long COVID being one, are not unique to SARS-CoV-2. I read that the Russian flu of 1889 was caused by a coronavirus. There are many anecdotal reports of people who suffered symptoms that appear analogous to Long COVID. The 1918 influenza pandemic caused an illness called "sleepy sickness." There are documented cases of post-polio syndrome afflicting people decades after their infection.

And most recently, there are published case reports of post-viral syndrome lasting several years after infections with SARS and MERS.

Persistence of the virus in an immune privileged environment versus immune inflammation and dysregulation, what do we know about Long COVID? And not just the symptoms it produces but why it happens?

SG: The honest answer is we don't. But the indications are that it's not just one thing. I think that much is clear. That's the reason why you see these post-viral syndromes with other viruses because it can't just be a viral determinant that's doing this because viruses are different. But it's probably a combination in terms of the constellation of symptoms that we see, it's probably a combination of potentially persistent virus in various reservoirs. And a long-term almost reset of immunity or misfiring of immunity that seems to be an issue. There you see the similarities with things like chronic fatigue syndrome and ME [myalgic encephalomyelitis].

But it is clear that SARS-CoV-2 ... there have been comparative studies with influenza, for example. It shows that the chances of developing post-viral syndromes are greater and the severity of those symptoms tend to be greater for SARS-CoV-2. Of course, those are just case studies in hundreds of patients rather than millions.

But it certainly seems to be the case that the Long COVID aspect is something like a ticking time bomb, to use that sort of quite lazy phrase, but it is going to be a major problem and it doesn't just affect adults. If you're talking about trying to get your economy back on an even keel and you're inflicting lots of chronic illness on a population, I don't understand the logic of that.

Because children [have it] as well. And I have a great focus on the plight of some young children that have developed Long COVID symptoms. I think this cannot be overlooked. It should not be overlooked. I know in the States this is a legitimate reason to claim disability support, which is great. I don't think we have that in the UK, unfortunately.

[Though the HHS claims that people with Long COVID can claim disability benefits, they are having difficulty meeting the evidence threshold insurers require. And the number of claims is creating a bureaucratic log jam. Estimates of severe Long COVID causing inability to return to work range from 750,000 to 1.3 million.]

But the etiology of it is complicated. I think there is good evidence that there are probably three or four different aspects. One, as you say, continued replication of a virus in a reservoir somewhere that's causing

sort of continuous triggering of immunity potentially. Second would be some kind of inappropriate immunology reset response that perhaps causes some level of autoimmunity or sort of consistent inflammatory activation status within the body.

Third is that we know that this virus can get in and damage different organs systems even following an acute infection that isn't particularly severe. We've seen reports about brains, hearts, lungs, livers and in the gonads as well.

And then there's also metabolic changes, which I think can be quite important. We've seen the development of insulin resistance and other metabolic changes in patients. And therefore until we get a grip on this, it's important to treat this as a syndrome and a syndromic illness, especially when people are trying to ascertain the incidence of these sorts of problems.

Many studies that we've seen in the UK and elsewhere have focused on just one or more of these symptoms in the population. It's not about that. It's about clusters of symptoms in syndromes that we have to account for which make their conclusions nebulous ... and, so, I think there's a lot of underestimations in terms of the incidence of Long COVID that's going on because some studies, as well intentioned and well powered as they are, but are not using the right control populations.

I do believe that Long COVID is more widespread than we think and could cause us bad long-term problems.

There are lots of calls for investigating therapeutics for this. But I think until we have more research on the actual cause that's going to be hard to do. We could start by checking different drugs to see if they help. It might be interesting to see what the incidence of Long COVID is in people who were treated with antivirals, for example, to see if there are differences there.

It's something that we need to look out for in the long-term, but, most importantly, it's something that we can reduce the incidence of by reducing the number of infections. The primary way of preventing Long COVID is to prevent the short version. It is encouraging to see that vaccines do help with Long COVID. People that have breakthrough infections with vaccines are less likely to develop Long COVID than de novo infections.

BM: Changing topics, I really would like your take on the Wuhan Lab Leak theory and gain of function experiments that have been pushed by the mainstream press.

Recently three important studies came out. One was from the Chinese CDC [Center for Disease Control and Prevention], the first international report by China, that tracked the infections among animal handlers at the Huanan Seafood Market. The other two were from Michael Worobey and Kristian Andersen. The first, using the data WHO had collected during their trip last year, they found that infections in the early stages of the outbreak, December 2019, clustered around the market. The second found that two zoonotic spillover events had to have occurred given the two circulating variants that existed at the time. They diverged considerably from each other in the context of how recent the outbreak was. Only a second spillover into humans could have explained their observations. Can you speak to these issues specifically or in general?

SG: I will quickly say, I don't think it was a lab leak. I think there's quite good evolutionary evidence for that. I don't think that it helped that the Chinese were slightly disingenuous at the beginning.

But I don't believe for the reason that you just said because of the multiple transmission events, that this was likely to be a lab leak. I certainly don't believe the virus has been engineered. That's my view on it really. The studies that came out the other week, I agree, are compelling.

I'd be very surprised if there was a leak. And even if there was a leak, it would be one of several transmission events. That doesn't mean that we shouldn't have tighter levels of restriction on gain of function experiments, however, I think you need oversight of that. But I think what

happened because of the arguments around influenza a few years ago, where you had embargoes on people's work and things like that ... that level of scrutiny was not productive. I think a good discussion needs to be had but the current regulations are pretty good. You need a lot of permissions to do any kind of work like that, but most gain of function studies aren't done generally anyway.

BM: As a final question, I'd like to reference a quote I recently came across by a giant in the field of modern public health, Dr. George Rosen. Back in the 1950s he said, "There can be no real comprehension of the history of public health at any period, without a thorough understanding of the political, economic, and social history of that period in its relation to the contemporary public health situation."

Pandemics don't just occur on their own without a social context. They're often potentially a byproduct of social decline. And to a great extent, the evolution of these variants to which you have spoken so eloquently have been aided and abetted by the national policies that have given SARS-CoV-2 ample opportunities to adapt.

Moving forward, how do we get out of this pandemic and prepare for the next one, especially in a world where the economy is globalized to a great degree, but being torn apart by significant national geopolitical tensions?

SG: That's interesting because during last week's session of the independent SAGE, we had Michael Marmot as a guest. [Professor Michael Marmot is an epidemiologist at University College London and the current director of the Institute of Health Equity.] He has been doing studies on inequality for many years now in the UK. And it's very clear that you can take the incidences of hospitalizations and deaths and overlap those incidences with things like illiteracy, the incidence of a requirement for dental fillings, of poor education, of malnutrition, of poor housing.

All these things are skewed towards inequality. We have this thing in the UK where we would clap for our key workers in 2020. And we have this government narrative around leveling up the UK. Michael Marmot made an important comparison between what's happening in the UK and the UK policy at the moment, what happened in Germany after the Berlin wall came down and how East and West Germany were reintegrated, and the investment level required to bring East Germany back on track.

I think it's fair to say that the scale of investment that's being proposed, and I'm just talking about the UK here, but I'm sure it's the same elsewhere, the scale of investment proposed that's apparently going to address inequality in the UK is nothing like what's required to really get to the crux of the matter. I completely agree. I think social inequity is a major issue with respect to any kind of pandemic or even endemic infection or indeed nontransmissible diseases. It's the same for obesity, for heart conditions. All these aspects have a strong sociological and socioeconomic factor, and you can only address that ... I'm not a public health person, but certainly the people I know that are, say that this is the major thing that you need to tackle if you ever want to get this to work better on an even keel.

And until we do that, we're going to continue to see a redistribution of this pandemic into the working class and the less well off.

I was fortunate to work from home during most of the pandemic. And I had family circumstances that made that necessary, but many people couldn't do that. And I think they deserve more than just a clap. Our health care workers, delivery workers and people who make the world function need to be better looked after.

And of course, people that don't have stable employment and good living standards are always going to come off worse. I completely agree with that statement.

And I think when the inquiry happens in the UK, hopefully, all these things will be addressed.

BM: Any final thoughts, Stephen?

SG: Since we had the availability of vaccines, the vaccines are our way

through this. But they shouldn't be doing it on their own. And if you're going to try and do that, then I think that's going to have a human cost, which some governments will be prepared to pay, and some will not.

I still stick to the idea that we need to vaccinate the world, but at the same time try to suppress the infections that are being caused by this virus across the planet. And until we do that, this is going to keep lasting all the longer for it, I'm afraid.

BM: I appreciate everything you've had to say on this.

SG: Thank you, Benjamin.



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