

Interview with Dr. Ziyad Al-Aly on the COVID pandemic and Long COVID

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This is the first part of a two-part interview. The second part of the interview with can be accessed [here](#).

Soon after the COVID-19 pandemic began to sicken millions of people, complaints of post-viral syndromes afflicting those who had recovered from the acute bout of infection began to appear on social media, and then in the popular press. At first these reports were anecdotal, but in May 2020, Elisa Perego, an archaeologist at University College London, created the term “Long COVID” as a hashtag on Twitter.

There remains no consensus definition of the disease due to the multifactorial, and as of yet not fully understood, pathophysiological process that causes the multitude of symptoms associated with Long COVID.

The World Health Organization (WHO) established a clinical case definition for Long COVID in October 2021 based on its understanding at the time, with the caveat that as new evidence emerged on the consequences of COVID-19 infection, there would be changes in the clinical definition to diagnose the condition.

The WHO wrote:

Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually three months from the onset of COVID-19 with symptoms that last for at least two months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time.

The British National Institute for Health and Care Excellence (NICE) and the US National Institutes of Health (NIH) and Centers for Disease Control and Prevention (CDC) have provided clinical criteria for post-COVID conditions that qualify as Long COVID. As of September 2022, the CDC estimated that 7.5 percent of US adults (15.6 million) were experiencing ongoing symptoms three or more months after their initial infection.

A recent published study in the *Lancet* synthesized the global evidence on the prevalence of persistent symptoms in a general post-COVID population and found that on average at least 45 percent of COVID survivors, regardless of the clinical course of their illness, went on to experience one unresolved symptom four months out. More than one-quarter complained of persistent fatigue. Among the hospitalized cohort, imaging and pulmonary studies revealed abnormalities and impaired functioning.

However, evidence of the impact of COVID infections on the health of the population remains sparse and a systematic analysis and study of the

long-term impacts of COVID infection and reinfection remain sorely lacking.

In this regard, the studies being conducted and presented in peer-reviewed publications by Dr. Ziyad Al-Aly and his colleagues have been critical in developing an insight into Long COVID. Dr. Al-Aly is director of the Clinical Epidemiology Center and chief of research development at the Veterans Affairs St. Louis Health Care System. Their findings underscore the dangers posed by SARS-CoV-2 infection and reinfection, regardless of vaccination status or severity of the disease after recovery from the acute phase of illness, particularly in damage to the heart, lungs and kidneys, and in metabolic diseases, neurological sequelae (after-effects) and mental health outcomes.

Dr. Al-Aly recounted in a recent talk he gave on Long COVID that when the pandemic first hit the country, “we as a research group in St. Louis started pondering what can we do as a group of researchers and physician scientists to address the challenge with the pandemic.” He added, “As clinical epidemiologists we started deliberating the best way we could contribute to the fight against COVID-19.”

Dr. Al-Aly explained that his group shifted to studying COVID-19. Out of this grew the recognition, brought forward by a coalition of patients afflicted with Long COVID, of the need to study this condition. He was surprised by the breadth of symptoms that affected so many organ systems. “This was a historic moment in the annals of medicine,” he said, “when patients came to the fore and alerted all of us scientists that something here is wrong and needs to be investigated and researched and gave the entity its name.”

But what is Long COVID, what are the true manifestations of the disease and how is it to be researched? The St. Louis group led by Al-Aly set out to address these questions in an unbiased manner, utilizing the Veterans Affairs Health System database. The group published its first report on Long COVID in *Nature* on April 22, 2021, titled “High-dimensional characterization of post-acute sequelae of COVID-19.” The report laid out the researchers’ extremely concerning finding that “beyond the first 30 days of illness, people with COVID-19 exhibit a higher risk of death and use of health resources.”

This was one of the first investigations into the long-term consequences of COVID infection, underscoring the dangers posed to the population beyond just the initial phase of infection. And the damage inflicted by the infection affected multiple organ systems, regardless of disease severity or age of the person. Perhaps most fundamentally, the report posed concretely the harmful relationship between communicable diseases and their potential consequences for population health despite the oft-repeated and scientifically unproven notion that the exposure of children and young adults to germs is good for them.

Dr. Al-Aly kindly accepted our invitation for an interview to discuss his work and the COVID pandemic.

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Benjamin Mateus [BM]: Good afternoon, Dr. Al-Aly. I hope you are

doing well.

Ziyad Al-Aly [ZA]: Yes, thank you. Delighted to be here.

BM: Thank you for taking the interview, Dr. Al-Aly. Your time is valuable. I have several questions for you but first I'd like to begin by asking you to tell us who you are, what you do, and your interest in Long COVID.

ZA: I'm Ziyad Al-Aly. I'm a clinical epidemiologist at Washington University School of Medicine, and the chief of research and development at the Veterans Affairs (VA) St. Louis Health Care System. And I direct the clinical epidemiology center here at the St. Louis VA.

Very early in the pandemic, we started seeing reports from patients and patient advocacy groups about patients who developed various symptoms after their acute COVID illness had resolved. Clinically, we were also seeing people coming back with lingering symptoms after what we all thought at the time was just an acute infection that if it resolves, it resolves completely in most people and does not really result in any post-acute or chronic sequelae.

But we started receiving those reports and that sort of launched us on a trajectory to understand what's going on with these patients. That led us to the characterization of Long COVID and on a pathway to try to understand the post-acute and long-term consequences of SARS-CoV-2 infection.

BM: Historically, we know that viral infections can lead to post-acute syndromes. Was there any thought at the beginning of the pandemic that this was a possibility, or were people just not aware of these or considering these issues? Maybe you can touch on these points?

ZA: Sure. I think hindsight is always 20-20. Now it's very clear to us that many viruses in human history have resulted in long-term consequences. But I have to also admit that we as a medical community or the community of medical professionals and people who deal with chronic disease and infectious diseases have generally ignored the idea that viruses can result in long-term consequences.

When initially SARS-CoV-2 hit I don't think it was at the forefront of our minds. At least it wasn't on my mind, although knowing, even dating back to the flu pandemics in the early decades of the 20th century, that flu also resulted in some long-term consequences in some individuals who were infected with the influenza virus. Still, I don't think that [clinical insight] was sufficiently hardwired in our minds when the pandemic hit.

Now, fast forward. Hindsight is 20-20. But what we're ultimately trying to tell people is that infections with viruses can lead to adverse long-term health consequences. This is a major concern, along with mortality.

SARS-CoV-2 is unique and at the same time not unique. It is unique because of its novelty at this moment, but it's not unique in the sense it's not the only virus in the world that can lead to long-term sequelae. We have had to almost rediscover this field in the wake of the early days of the pandemic.

And I think an important lesson to take going forward from all this is that we must recognize that pandemics are going to happen. These are one of the certainties of life. Pandemics are going to keep happening and there are going to be pandemics down the road, and we must recognize that pandemics are not only cause acute events, but they could in some instances lead to long-term serious manifestations, which can have enormous consequences not only on health outcomes, but potentially on the economy and societal well-being.

All this means, going forward, is that we must think about how to learn from this pandemic and be prepared for the next one. One key step is to evolve our data systems—our data systems need to be able to capture all this information needed to help us assess the toll of post-acute and long-term effects of emerging infectious diseases.

BM: Has anybody ever compared the post-viral syndromes between SARS-CoV-1 and SARS-CoV-2?

ZA: No, not to my knowledge. I think that this is really to your point,

Benjamin, is that we haven't really invested in or thought sufficiently about the post-viral condition to fully characterize different viruses and their long-term consequences, nor do comparative analyses to try to understand similarities and differences in the long-term adverse health consequences of different viruses.

So, what are the consequences of SARS-CoV-1, SARS-CoV-2, and MERS? What about Ebola and post-polio? And post flu? And we draw quite a bit of comparison to COVID versus flu, but I also have to admit, what are the five-year outcomes of COVID versus flu? Does anybody know the answer? It's not known. Look, the flu has been around a very long time, meaning we should know these things, but we don't. It's been around for more than a hundred years, but we've also ignored it for more than a hundred years.

And as a result, when you ignore something, you don't have a lot of knowledge about it. So going back to your question of SARS-CoV-1 and SARS-CoV2, there isn't a whole lot of data out there that can give us a full view for a comparative analysis or the long-term consequences of one versus the other.

BM: Regarding ME/CFS—myalgic encephalomyelitis/chronic fatigue syndrome—is there a better understanding now that this may be a post-viral syndrome that has manifested in a blanket name for this disease, whose pathophysiological mechanisms are poorly understood?

ZA: There are many hypotheses on ME/CFS, which has been talked about for more than 30 years. But it has been substantially underfunded and therefore not sufficiently studied. One of the hypotheses of the pathobiology of ME/CFS is that it's initially triggered... or the initiating event is a viral infection.

So, what is the virus that initiates ME/CFS still needs to be clarified. But many of those patients, when they are eventually diagnosed with the condition, when they track back the origins of their symptomatology, in a lot of these patients the triggering event is an upper respiratory tract infection or some sort of an infection with fever that only lasted a few days or just symptoms of a cough, some shortness of breath and sore throat for a few days... what we generally classify broadly under the umbrella of an upper respiratory tract infection or the symptomatology that overlaps substantially or what we commonly refer to as upper respiratory tract infection. It's at least clear from those data that that maybe the triggering event is a viral infection.

But I also caveat that by saying that the science on that is not definitive. The identity of that virus has not been pinned down. Still, all of this speaks to the notion that we are talking about, that these entities may have a viral origin and they could be broadly classified under the post-viral illness category, or more appropriately called an infection-associated chronic illness. That's the term that most people prefer to use. There are different terminologies, and the field is still nascent and evolving but presently the most accepted term is infection-associated chronic illnesses.

However, those baskets of conditions, including ME/CFS, have not been sufficiently studied for us to sit and have a conversation without the data being available to review. The short answer is that we don't really know conclusively if ME/CFS is initiated by a virus and then which virus. But plausibly, there are hypotheses suggesting that may be the case.

BM: Which raises the topic that has captured the attention of the mainstream press and social media, that is, the pseudo-scientific construct of immunity debt. Additionally, many people, whether they're politically reactionary or they just don't know, think that getting infected is somehow good for building your immunity. Within the confines of long COVID and these post viral acute syndromes, what would you tell someone who raises those issues?

ZA: Sure. I hear that a lot and I hear people saying that "a cold never really killed anyone!" And it is true that getting a cold doesn't really kill anyone [immediately]. But I would like to ask the question, "Does a person who gets, between the ages of 20 and 50, if they get five colds and

another person with the same characteristics gets 20 colds, do they have the same risk of cardiovascular outcomes or neurologic outcomes?"

And the answer to that is that we don't really know. People trivialize infections because they don't really see immediately the [long-term] consequences of infections. That's not only true for SARS-CoV-2, but also for a lot of other infections. Even going back to the mildest infection that people generally try to trivialize—the common cold—but we don't really know what repeat infection means for the life of a person, though we should. Are those people who have more colds at higher risk of long-term disease?

BM: These are important questions and in the context of the pandemic not inconsequential.

ZA: And I would posit, based on some of the evidence we have obtained from our studies, I would hypothesize that the person who gets more infections actually has a higher risk of long-term outcomes, even with a cold.

People trivialize these things without really knowing that there are phases of infection, and it may be true that in the acute phase, if you're only observing for a few days after an upper respiratory tract infection with a common cold and they quickly bounce back and seemingly on the surface there is no real damage, we can't be certain on the long-term impact it will have on their health.

We really don't know, but this is really what we need: more understanding of repeat infections.

Now, with SARS-CoV-2, we know because we've done some work to characterize these risks between one, two or three infections. And it is abundantly clear that the people who got hit twice or three times with COVID have it worse compared to those with only one prior infection, both in the acute phase and the long-term phase or post-acute viral phase.

So I think that this idea that infections provide you with immunity and that's going to shield you and it's going to totally offset the long-term cost of an infection is bizarre to me. It's too simplistic and wishful thinking. I wish this was true—to be a kid in a candy store trying to imagine life like that. It would be nice to get one infection that would immunize us from subsequent infections and carry no further risk—it would be wonderful, but that's simply not the case at all, at least for SARS-CoV-2.

BM: Just one more question along this line before circling back to something you mentioned earlier. What is the latest hypothesis around the mechanism behind post-COVID syndrome? Is it the persistence of the virus? Is it immune dysregulation? Is it a vasculitis and micro-thrombi?

ZA: Brilliant question, Benjamin. But the short answer is we still don't definitely know with absolute certainty. There are multiple hypotheses and many interesting experimental works that are being done by researchers throughout the world on this question.

One central hypothesis suggests the idea of viral persistence in "immune-privileged sites." And when we say viral persistent, it doesn't mean the whole virus but fragments of the viral RNA or proteins that reside in immune-privileged sites that provoke chronic inflammation. That hypothesis is plausible, but it still remains in the realm of a hypothesis, meaning it would still need to be supported with evidence or refuted with evidence. That's what hypotheses are—a line of thinking that would need to be tested experimentally and clinically to validate whether it's true or false. In other words, we would conclude that a certain hypothesis is not valid based on A, B, C, D, and E evidence.

At this point, I still classify viral persistence under the umbrella of a hypothesis. And there are a lot of other hypotheses that have been presented. One of them, as you pointed out, is immune dysregulation. Another revolves around the idea of a microbiome dysbiosis. This idea that within us, within the human body, there are more bacteria than human cells. And with viral infections, these microbiomes are disturbed, causing "microbiome dysbiosis," which then provokes a state of ill health or

disease. Again, all of those are hypotheses.

I also have to say that they're not necessarily mutually exclusive. The idea there could be immune dysfunction does not really exclude the possibility that viral persistence or microbiome dysbiosis is causing chronic inflammation or a state of disease.

When we speak about Long COVID, and we both have studied it and thought about it deeply, to know it's not really one thing. At the end of the day, it's unlikely to be one thing. We can certainly classify it under the broad umbrella of post-acute illness or post-viral illness. That would be correct. But I think we have to be reluctant to oversimplify a complex condition like that and make it one thing. It's unlikely to be just one thing.

When I speak to the "lay press" I give the example of our conception of cancer a hundred years ago, when we lumped all cancers under one category—this is tumor outgrowth or this is cancer—but we now know that there are more than 800 types of malignancies and all have different genomic signatures and different responses to treatment, and so on.

In that sense, the field of Long-COVID [and post-acute viral syndromes] is really that nascent or that embryonic in the sense that maybe ultimately, over time, we'll recognize Long COVID type A, type B, and type C with different manifestations, different responses to treatment, and also different pathophysiology on different mechanisms, meaning, that some of it, maybe Type A, is driven by viral persistence, but type B is driven by microbiome dysbiosis.

The field is nascent or embryonic, which means we have to have an open-minded approach to it and learn from the evidence and adjust our thinking accordingly.

To be continued.



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