

# Interview with Dr. Ziyad Al-Aly on the COVID pandemic and Long COVID: Part two

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*The first part of this interview with Dr. Ziyad Al-Aly can be accessed [here](#).*

BM: I'd like to return to a point you raised earlier, and this next question gets to the heart of the work that you and your colleagues have done with multiple studies on neurological outcomes, metabolic disorders, cardiovascular complications and the reinfection and breakthrough infection ... you have access to the database at the VA health system and the medical records of millions of patients which have provided you with critically accurate data. This has allowed you to draw these important conclusions about the nature of acute and late-phase COVID infections.

In your discussions with your colleagues at other institutions, what is the state of the database, having good, reliable long-term data in the US? Do we have precise data to help us make such important observations as your team have?

ZA: I think this is one of the learning points of this pandemic. Our data systems ... the VA is what I consider a pioneer and I feel lucky to be at the right place at the right time and having access to the data and leveraging our experience with data analytics to help address public health questions of great importance in a timely fashion. That has been the confluence of a lot of factors that made it a success, allowed us to do what we do and really inform the public, give the public information to help navigate the pandemic.

Unfortunately, the VA is a bit unique in this regard, and it shouldn't be. What do I mean by that? The data systems at the VA are sufficiently evolved and of high quality to allow us to do what we do. But we shouldn't be the only player in town to be able to do such analyses. More data systems throughout the country should be evolved in a similar way. But unfortunately, the reality on the ground is they're not. But this is another opportunity to create these systems because they are going to be important to address major questions in future pandemics.

Again, I have to say this, the VA isn't the only data system available, but the maturity of the VA data system is far more advanced than other health systems where their data is very fragmented and all over the place, meaning their data quality is subpar. It shouldn't be the case but that is the reality.

More broadly from a public health policy and infrastructure perspective, I really do think that surveillance systems for emerging pathogens should also be evolved to capture the long-term consequences of infections. Currently the data systems that we have at the CDC in the US, and everywhere in the world all have pretty much the same problem, the same blind spots everywhere.

BM: Dr. Al-Aly, regarding the recently published reinfection study, what would be some of the major takeaway points you would emphasize to the public? What were the findings that struck you as most surprising or most interesting in that study?

ZA: I think the most important thing is that for people to really understand is that two infections are worse than one, and three are worse than two. We were trying to make that as clear as possible to people.

We're not necessarily saying that a second infection could be milder or worse than a first infection. What we want to emphasize is that if you had the misfortune of being infected once, it's definitely better for your overall health to avoid a second infection.

So, just to repeat, two infections are worse than one and three infections are worse than two. And when I say worse, it's worse both in the acute phase, meaning in the first 30 days, and also in the post-acute phase, meaning in the Long COVID phase or beyond the first 30 days of illness.

Maybe early in the pandemic, the scale of Long COVID and the scope of the problems that we and others have characterized used to shock me. I described it several times as jarring to recognize that people would have heart problems and neurologic disorders, etc.

But at this point I don't think there was anything about the results of the reinfection study that was so implausible that it struck me as surprising, although the data is very disturbing to say the least. I know a lot of people did not want to accept that. They wanted to still believe that the second infection is inconsequential. I'm familiar with that sort of pushback. But the data we published is quite clear.

Two infections are worse than one and three are worse than two.

And what that really means is the continued emphasis on reducing the burden of infection and reinfection is going to yield the greatest public health benefit. Now some people argue that the cost of mitigation might outweigh the benefit. That's not the debate that this paper created or intended to create. What we said is if you want to achieve the best public health benefit for your people then mitigation measures that reduce the risk of infections (whether first infection or reinfection) are very important.

But soon enough a lot of people around the world, unfortunately, will have had a first infection. China is heading in that direction. By some estimates in the US more than 80 percent of the people have been infected at least once.

BM: I think the other critical finding in your study was that it didn't matter if you were previously vaccinated. Reinfections do similar harms among unvaccinated and vaccinated, correct?

ZA: That's very important. That's correct.

I should really preface this by saying that the reason we did the [reinfection] study is that we started seeing people here in the VA clinic coming back with this air of invincibility. They had been vaccinated and previously had COVID-19. They would come back to the clinic and say, "I've had Covid 19 before and I'm also vaccinated." They started picking up reports in the media calling them "super immune" because the media started referring to these patients as having some sort of super immunity,

meaning they had vaccine-derived immunity and natural immunity from a prior infection.

Some people latched on to this concept of “I’m super immune. The press is telling me I’m super immune.” It’s all over the news. But, and it’s very clear in our data, that even if you’ve been vaccinated and you had prior infection that “super immunity” is not super immunity. If you get infected again there is still an increased risk of death over people who didn’t get reinfected. There’s still an increased risk of health problems both in acute and post-acute phase. That super immunity is not really a perfect shield. In fact, there is nothing super about it.

A more appropriate term for this would be hybrid immunity or immunity from both sources: vaccine-derived immunity and immunity from prior natural infection. I prefer the term hybrid immunity over super immunity, that sort of colloquial term used by the media that has engrained itself into the minds of some patients.

And that was precisely why we started thinking about these people. I started thinking, “Are these people truly super immune?” Because they had this air of invincibility about them. They would come to our clinics and even though we maintained a universal masking policy, which I am very grateful for, they would come to the clinics and say they didn’t want to mask because they were super immune. I started asking the question, “Is what they are saying credible? Are these people super immune?”

And the answer from the data is that they actually are not.

BM: Listening to you and having read your paper and studied your other publications on these topics, in the context of how the US has responded to the pandemic, the various iteration of herd immunity, learn to live with it, and forever COVID, any thoughts about these statements that are made by politicians and various figures in the public arena?

ZA: These sound like what I classify as aspirational thinking. Listen, we all want the pandemic to be over. But the fact is that the pandemic is not over. You just have to pick your news outlet of choice and tune in to what is happening in China. And you will quickly learn in stark images that the pandemic is *absolutely* not over. [Emphasis by ZA] I think a reality check is important here.

There’s a difference between reality on the ground and what we desire. It would be wonderful when the pandemic is truly over. Most people on Earth, if not everyone, would like to see this pandemic come to an end. But the reality is that the pandemic is still raging ... in the US ... and even more now in other parts of the world. Even more intensely in other parts of the world. [Japan is presently facing the highest COVID mortality rates than at any time during the pandemic]

We must deal with reality and the reality check is that there are tons of people in the hospitals here and many in the ICU and on ventilators from SARS-CoV-2 infections. The pandemic is not over, if you look at the facts.

BM: I wanted to ask how Omicron plays into the findings of your studies as people have claimed that Omicron is mild? Are you continuing to analyze your data with different variants?

ZA: We have a pipeline of studies and we’re looking at many aspects. We have quite a robust agenda and we will be continuing to work on these. We’ve certainly done a bit of work over the last two years looking at Long COVID.

We’re interested in characterizing the longer-term health trajectories of people with Long COVID beyond the first year. We’re interested in tracking variants and their effects, and not only Omicron. We are very cognizant that the explosion of cases in China might lead to a new variant of concern. There is obviously the XBB and potentially other variants that may take hold.

[XBB and XBB.1 are derived from the fusion of two different BA.2 variants—BA.2.10.1.1 and BA.2.75. XBB has evolved into XBB.1.5 and its F486P key mutation that provides it the most growth advantage versus BA.5 and a much higher ACE2 binding affinity making it even more

*transmissible and potential for sustained growth. Immunobiologist Dr. Akiko Iwasaki from Yale School of Medicine recently warned, “I am truly concerned about the Long COVID wave that follows this infection.”]*

And those new strains of SARS-CoV-2 may have different pathogenicity profiles and therefore Long COVID profiles. That will require tracking and close attention to understand these nuances more deeply. These and many other questions down the road are what we are thinking about and brainstorm quite extensively about. And some of these become agenda items we begin working on. There is quite a bit in the pipeline.

We are also very interested in therapeutics. We completed a study recently showing Paxlovid helped reduce the risk of post-acute sequelae, AKA Long COVID. More than characterizing Long COVID, we need to understand if the use of therapeutics in the acute phase of the infection, in the first 30 days, can influence the risk of short-term and long-term events. There’s quite a bit in that area we are working on. But we aren’t a huge group, and we are working pretty much day and night to try to address what we think are questions that can help the public.

BM: I think the work that your group is doing is exceptional and very important.

The CDC recently reported on life expectancy in the US in 2020 and 2021 with two consecutive years of decline. Now we are also seeing hints of higher excess deaths than pre-pandemic baselines coming in from various countries like Australia, Peru, and Europe. We’re seeing higher rates of heart attacks and strokes. In the context of our present discussion, do you think these are attributable to mass infection and reinfection with COVID? Is this a byproduct of the stress on our health systems? Is this undercounting of COVID deaths?

ZA: I think the answer, as you suggest, is multifactorial.

We’ve been worried about this, and I was hoping that our prediction on these would not pan out. I wrote two years ago that the COVID pandemic risks reversing much of the progress in public health, in global health, and improvement in life expectancy we had witnessed over several decades. And now, we are seeing those same exact things happening. We are seeing an unprecedented reversal in life expectancy of the kind not seen in the past 50 years since the world decided to track life expectancy.

It’s remarkable to witness how this pandemic has reversed so much of the hard-earned progress that we’ve made. Not only in the US but in many countries around the world.

Now, you’re asking what is it attributable to? It’s apparent that it is driven in a large part by the pandemic. And some of it could be directly attributed to SARS-CoV-2 itself. The idea that SARS-CoV-2 can lead to long-term manifestations in people and lead to excess death not only in the acute phase, but also in the long-term phase through heart attacks and neurologic dysfunctions all of which are associated with higher risk of death or lead to higher risk of death. And then there could be other factors.

But, to the point, life expectancy is the major indicator for health. It’s one of the major metrics if not *the* metric for the health of a population. And progress on life expectancy is hard-earned. It takes a lot to move it in the right direction. And if you really track the numbers over the past 50 years, it has been inching up and up in the US and a lot of other countries throughout the world. It takes a lot of effort to really move things in the right direction.

And then you have this COVID pandemic, and you suddenly take this massive dip, a decline in life expectancy, reversing a lot of the progress we had made. And that’s quite alarming to see.

We wrote about it a couple years ago at the very beginning of it all saying that the mismanagement of the pandemic risked erasing a lot of the progress in public health. And, unfortunately, it seems to be happening as we had warned.

BM: I have one last question for you, Dr. Al-Aly. There was a study that

came out looking at the population of California and ranking them by the economic deciles and life expectancy before the pandemic and then through the pandemic. I found it disturbing that even before the pandemic there was a ten-year gap in life expectancy between the poorest and wealthiest. And during the pandemic, the poorest saw life expectancy drops almost five more years while the richest barely dropped if at all leading to an overall 15-year gap. In other words, when we look at life expectancy, the socioeconomic conditions tell a different story through the tracking of this data. Could you comment?

ZA: That's unfortunate, although I haven't read the study you are referencing. But it is consistent with our understanding that the most vulnerable among us and the most disadvantaged among us are generally the hardest hit. And in situations like the pandemic, sometimes in the field called mortality shocks or discontinuity events affect the most vulnerable people. It disproportionately affects disadvantaged populations more and widening inequity.

Even before coming into this pandemic there were clear inequities and life expectancy differences in the US. You could drive 10 to 15 miles between two counties or zip codes and life expectancy dropped by 10 years or more. That's profound. There are clearly very significant disparities at play. But the pandemic is risking widening these inequities and disparities further.

BM: The other inequity I wanted to raise is that of age. Maybe it is an odd way of putting it, but we are seeing more than 400 COVID deaths per day and it is killing people over 65 at an alarming rate despite their vaccination status. More than 90 percent of all current COVID deaths are among the elderly. Your thoughts?

ZA: Our death counts these days is not the best and I worry that we are missing quite a bit of data. Maybe it's disproportionately reported and or tracked or attributable to COVID in the older population such as in nursing homes. I don't want to make too much of that, but I think it's generally clear that big events like the pandemic stress the system; all of it.

Parts of the system that are more resilient, generally the people that are well resourced, wealthy, advantaged and have access to resources, they are more resilient and they're going to fare better. And that's really the reality of the system that creates an uneven landscape where some people could be more resilient than others. And I think in general what you want is really an equitable system that empowers all people to be able to cope with these challenges. Because pandemics are going to happen. You should aim to preserve health for all the people equitably.

BM: Thank you so much for this opportunity to sit and talk with you. But before we conclude, any final points?

ZA: I don't, Benjamin. This was very thorough. You asked me all the major points and I very much enjoyed talking with you. Thank you.

BM: It's been my pleasure. Please give my compliments to your colleagues. I know the kind of work that you do requires a very strong, cohesive, and dedicated team. And from my perspective, I think the work you do has been invaluable.

ZA: Thank you for that.

*Concluded*



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