

## Episode 99: A Time for Humility

**Chris Dall:** [00:00:06] Hello and welcome to the Osterholm Update COVID-19, a podcast on the COVID-19 pandemic with Dr. Michael Osterholm. Dr. Osterholm is an internationally recognized medical detective and director of the Center for Infectious Disease Research and Policy, or CIDRAP at the University of Minnesota. In this podcast, Dr. Osterholm will draw on more than 45 years of experience investigating infectious disease outbreaks to provide straight talk on the COVID-19 pandemic. I'm Chris Dall, reporter for CIDRAP News, and I'm your host for these conversations. Welcome back, everyone, to another episode of the Osterholm Update podcast. They say all good things must come to an end, and that statement could apply to the COVID-19 situation here in the United States. After several weeks of decline and plateau, the national seven day average of COVID-19 cases has begun to tick upward, driven mainly at this point by rising BA.2 infections in northeastern states. The increase at this point appears to be small, and how much cases will rise over the coming weeks is still unclear, but the arrow is nonetheless headed in the wrong direction. Meanwhile, although many nations in the Western Pacific region are continuing to decline from their Omicron peaks, China remains a house on fire and the government's zero COVID approach appears to be wearing on the public. Those will be among the topics of discussion here on this April 14th episode of the podcast as we assess the state of the COVID-19 pandemic in the United States and around the world. We'll also talk about some of the latest news on fourth doses of COVID-19 vaccines, answer a COVID query about rapid home testing, and share the latest beautiful place submission from one of our listeners. But before we get started, as always, we'll begin with Dr. Osterholm's opening comments and dedication.

**Michael Osterholm:** [00:01:52] Thank you, Chris. And welcome back to all of you to another edition of the podcast. We're so glad to have you with us. For those who may be first time listeners, I hope that the information we provide to you today is helpful, that you might want to join us again. And of course, for those who have been regulars, part of the podcast family, thank you for coming back again. We thank you for your feedback and for your many wonderful, wonderful comments. And I say wonderful in the sense that you often challenge us. You ask us good questions and you make us better. And we appreciate that so very, very much. And at the same time, we not only share our heads with you, but as you know, we have shared our hearts. And today, actually, my

dedication is in part tied to a combination of the head-heart issue. We're going to get into all kinds of challenges with regard to understanding what's happening with the pandemic and what it means for us going forward. But I'd like to take a step back right now. I'd like to take a step back to something that has happened already. And I'm dedicating that what has already happened to a very, very special group. Over the course of the pandemic, we've all found our ways to survive. And I mean by survive, not just physically, but emotionally. And I will start out by saying that this particular dedication is unusual. And frankly, though, it's something that is so heartfelt for many of you. And I know that to be the case. I am one of those people who feel this particular sense of dedication. Over the first year of the pandemic, it's been estimated that there have been 23 million families that have adopted a pet to help them be part of the family of the response to what they deal with with this regard to this pandemic. No one, I think, can ever overstate the critical importance of companion animals. There is nothing that can mean more than coming home from a long, long day or for being closed in for days and days then to see that companion animal so overjoyed to see you or to be with you. And anyone who has lost a companion animal really can put this into context because of what it means to lose them defines what it meant to have them. And so today I'm actually dedicating this podcast to all those companion animals that so many of us I say, quote own in quotes, because in a sense, we never really own them. We're part of the caretakers for them. They, in a sense, really own us. And they have provided us with such critical, critical support during this very difficult time. And I will go one step further to say, I, for one, happen to know first hand the importance of a companion animal and what it means to me. It was actually just over six years ago, six years ago, on April 10th, I lost my Max. If any of you have seen my backdrop over the course of the past two years you see a picture back there of an Australian shepherd, Max. I had Max for almost 14 years. Max was smarter than me in many instances. We would, for example, go to a trout stream property that I owned in northeast Iowa, and it was one of those most beautiful places. And if Max saw me in a suit and tie and a suitcase, he knew I was going to work somewhere else and he would sit in a corner and ignore me. If he saw that I had blue jeans on or cutoffs or something like that and a suitcase, he knew he was going and you could hardly contain him. There were so many, many hours over the course of those 14 years that Max was, in fact, unconditional love. So today to all the companion animals who have helped get us through, who continue to help get us through, thank you. Thank you. My dedication. Well, I can't close out the opening, Chris, of course, without also giving that glimpse of sunlight, the optimism that we all want to

feel right now for those of us in the northern hemisphere in particular, is substantial. Today, April 14th in Minneapolis, Saint Paul, we will have 13 hours and 27 minutes and 20 seconds of sunlight. Almost 21 minutes have been gained since our last podcast a week ago. And of course, we are far, far beyond now that winter solstice of December 21st of 8 hours and 46 minutes. But we're not done. We've still got a couple more months to go to add light. And I hope for all of us in the Northern Hemisphere, we can feel that growing light presence and the fact of what it means in terms of feeling that kind of recovery from the darks of winter. And for those of you in the southern hemisphere, we got you covered. We're sending as much light as we can to you. So, again, thank you all for being with us. And if you thought the dedication was a little bit crazy, I will not apologize because there are many of you who will understand that. And I hope that you can go and hug your companion animal just as you hug your kids, your grandkids, your friends, your neighbors and realize what a gift they are at this very, very difficult time.

**Chris Dall:** [00:07:24] Mike, let's start where we started the last few weeks, in China. Residents of Shanghai, which is now entering its third week of lockdown, are growing increasingly frustrated with the zero-COVID strategy, but the government appears committed to it. How long do you think they can maintain this approach?

**Michael Osterholm:** [00:07:42] Well, as I've shared before, Chris, trying to stop any and all cases of Omicron is a lot like trying to stop the wind. It's not going to happen. Of course, there are ways to divert it, which can play an important role in limiting the damage. But that's quite different than attempting to stop it dead in its tracks. This is what China seems to be set on trying to do. I think it's only a matter of time before we see China pivot from its current zero-COVID strategy. However, I'm not exactly sure when this will happen, and I couldn't exactly tell you what it will look like. Now, that being said, I certainly don't envision a situation where we'll see China suddenly up and lift all restrictions that are in place. Obviously, I think it would be a lot more subtle than that. But overall, I think we will see adjustments being made in the days ahead. Remember, just one month ago, their National Health Commission approved the use of a rapid at home test by members of the public. On top of that, they changed their treatment guidelines, which up to that point required all cases, regardless of symptom status, to be admitted to a hospital. Instead as a result of the change, asymptomatic or mild cases could now isolate in separate facilities. So what prompted these decisions?

Well, for the most part, I think they were made out of necessity. In other words, China's access to resources, which in this case included PCR testing and available hospital beds as well as critical health care staff was clearly being challenged. So we've seen them tweak their approach in situations where they've recognized their limitations or vulnerabilities. In fact, one could argue that their occasional reliance on more focused or targeted lockdowns, which they used in Beijing around the time of the Olympics and in the early days of the Shanghai outbreak, was another example of officials there acknowledging that sweeping, heavy handed zero-COVID policies came at a real significant cost. So instead of immediately sealing off entire cities, they opted to first seal off selected buildings or neighborhoods. However, despite these changes, we have yet to see officials there, formally or even subtly move away from the country's zero tolerance approach. Instead, we've seen them double down. Even just this past week, a leading Chinese health official asked residents of Shanghai to not let down their guard. He later went on to say that, quote, "lying flat is not an option for China," unquote. Rallying cries have also recently been featured in some state run news outlets, with one imploring residents to, quote, "draw up their swords and fight against all kinds of behaviors that interfere with the situation," unquote. And finally, there are even reports of drones flying around Shanghai and requesting residents to comply with restrictions. So as you mentioned, Chris, the government there clearly seems committed to this approach. As like I said in last week's episode, it's not all that surprising given the political reality of the situation and the remaining gaps in protection across their population, particularly among the elderly. There are still more than 40 million, let me repeat that 40 million Chinese residents, 60 years of age and older without a single dose of vaccine. On top of that, there are many more in the age group who have yet to receive the critical protection conferred by a third dose of the inactivated Chinese vaccines. But at the end of the day, it all comes back to the notion of trying to stop the wind. We've known for months what Omicron is capable of, and some of us have recognized the threat posed to China. Again, as Zeke Emanuel and I wrote in our New York Times op ed this past January, commitment to a zero-COVID strategy means that China will always be chasing an ever moving target, and they will never win. It's not for lack of trying, it's just the reality of the variant. So while I completely understand that there aren't any easy solutions for China, I think they'd benefit from acknowledging this reality and doing whatever possible to foster a more balanced and sustainable approach. According to a Reuters article published this past Monday, similar thoughts were recently shared with Chinese officials in a letter from the European Union's

Chamber of Commerce in China, which provided examples of the country's policy disrupting European businesses. As an example, the letter mentioned results from a survey by the German Chamber of Commerce, which found that nearly half of German companies were experiencing severely or completely disrupted supply chains due to the current situation in China. Let me just repeat that. They found that one half of all German companies were experiencing severely or completely disrupted supply chains due to the current situation in China. The letter later went on to say that the old toolbox of mass testing and isolation was no longer capable of overcoming challenges presented by Omicron and called for revisions such as embracing and distributing available mRNA vaccines that were developed outside of China. Coinciding with the news of this letter were orders from the US Department of State for all non-emergency government staff in Shanghai to leave, citing the ever changing arbitrary enforcement of laws and restrictions there. Regardless, the country's overall approach has largely gone unchanged, and as a result, there are now an estimated 45 Chinese cities under full or partial lockdowns, representing more than a quarter of the country's entire population, which helped contribute to just over 40% of China's annual GDP. On Tuesday, the country reported another 27,500 locally transmitted cases. Although a majority of these were from Shanghai, which I'll cover in a bit, there were nearly 30 total provinces and municipalities across the country with cases. This includes Jilin province, which reported another 1,000 cases despite being locked down for more than a month, and Beijing, where cases have popped up in high risk neighborhoods. In addition, a couple of dozen cases were recently identified in the city of Guangzhou, prompting officials there to restrict most new arrivals into the city of 18 million, which also happens to be home of China's busiest airport. While lockdowns haven't been implemented their schools have moved online, and citywide testing will be kicking off shortly. Even residents of Wuhan are seeing restrictions tighten after a dozen cases were released and reported there. And finally, there's Shanghai. Although the city of 26 million has been locked down now for three weeks, more than 23,000 new cases were reported there on Tuesday. For context, at the time of last week's episode, Shanghai reported 13,400 daily cases. At this point, more than 200,000 cases have been reported from the city during this wave. However, according to health officials, there have been no deaths and just one case is currently considered severe. As I mentioned last week, this conflicts with the on-ground reports. I just had an opportunity yesterday to speak to a reporter who's actually on the ground in China and they were convinced that there had been many, many more deaths than being reported by the Chinese officials. I am absolutely convinced that they are, in

a sense, cooking the numbers right now. There is no other explanation for it. Think about what happened in Hong Kong. There, where there was transparency, we now have a country that has the single highest documented mortality rate for COVID deaths of any country in the world. They went from being what was considered to be the ideal or model example to one of the worst. I do not understand how that will not occur inside of mainland China. So what's happening now? Well, there have been widespread reports of continued and worsening food shortages, limited access to medical care and ongoing economic disruptions. This past week, Shanghai city officials reportedly announced a phased exit to the lockdown. For the 4.8 million residents living in newly designated prevention areas, which are neighborhoods that have gone at least two weeks without cases, this meant that they could leave their homes as of Tuesday and even visit other authorized neighborhoods. As for the 1.8 million living and control areas where new cases haven't been detected in the past week, residents could leave their homes but had to stay in their neighborhoods. However, for the 15 million living in quarantined areas, which are those places that did report cases in the past week, residents are still confined totally to their home. So again, with more than half of the country's financial hub stuck in their home for weeks and no clear end in sight, I really don't see how this commitment to zero-COVID is sustainable. And I worry that until China acknowledges this new reality that we've entered with Omicron, the ripple effects will only grow into tsunamis as supply chains around the world are severely challenged.

**Chris Dall:** [00:17:00] And what's the latest on the BA.2 wave in Europe?

**Michael Osterholm:** [00:17:05] Well, overall, the recent wave in Europe appears to be continuing to subside. Average daily cases for the region as a whole have dropped from around 750,000 a day in mid-March to around 500,000 a day now, the lowest they've been since December. In addition, their death toll has declined for the eighth straight week, sitting at around 10,350, far below the 26,600 reported in early February. Now, let me be really clear as I discuss the situation in Europe, what you have here are many different countries with many different experiences, all being added together to define what's happening in Europe. I think that is kind of like saying your head's in the freezer, your feet are in the oven and on average, your temperature is just right. We have to really look more carefully at what's happening in many locations in Europe to understand the complexity and frankly, the confusion of what is being experienced in Europe means for places such as the United States. So notwithstanding any regional

improvements which surely shouldn't be minimized, there are still a number of countries in Europe dealing with challenges driven by the latest wave. In fact, if you look at the Washington Post list of the world's top 12 countries with the highest per capita case rates over the past week, at least as of this past Tuesday, you'd find that there were eight in Europe. In addition, when it comes to per capita death rates, ten of the world's top 12 countries with the highest numbers were again located in Europe. So it's another reminder of just how drawn out the recovery phase can be even after a peak is reached. A story published in the British Medical Journal this past Monday added more context to this reality, using England as an example. According to the article, the country's health care system continues to be challenged by COVID. In early April, a hospital and ambulance service in the country declared critical incidents. In a statement, the hospital, which has nearly 1,000 beds, said the following, "Our beds are full and our emergency department remains full, with patients requiring admission. We are only able to treat patients with life threatening conditions and injuries." The story goes on to say that this isn't just a one off, isolated situation of the country. Numerous hospital trusts are reporting up to 12 hour waits in emergency departments, and more than a quarter of ambulance arrivals nationwide in early April were delayed at least 30 minutes, making the worst performance on record. In addition, an average of more than 71,000 staff in acute care facilities were absent each day due to illness earlier this month, with 40% of those absences attributed to COVID. As the chief executive of England's National Health Service Confederation put it, the brutal reality for staff and patients, is that this Easter in the NHS is as bad as any winter. He added the following, although we're much better at dealing with COVID than we have been in the past, fewer people die, fewer people end up in intensive care. It is still a disease that puts immense pressure on the health service. It is adding to the demand which already exists partly due to the number of people who are waiting for treatment which built up during COVID. So it's important to remember what these surges can and do mean, even if they don't necessarily appear as dramatic on an epi curve or a dashboard. And if it's happening in the UK, it can and will certainly happen elsewhere. However, I think the challenge is that we're back to a position of not necessarily knowing when and where it will happen. Again, we are seeing numerous examples of places in Europe where BA.2 has taken over as the dominant variant, but cases have only continued to decline. We have situations in countries where cases are rising and yet BA.2 is not. So I don't think that we have a clear cut formula or blueprint to rely on these surges. There is no pattern in Europe which provides a really well-defined roadmap for what will happen in the US. It could be

much as is being seen in the United Kingdom a substantial challenge. It could be what we're seeing in these other countries where in fact case numbers are not rising related to the BA.2 presence. So let me just say whether it's in the form of BA.2, or some new variant or lineage like BA.4 and BA.5, which we're still learning about and we'll discuss next week. This virus still poses a threat to the world and our battered health care systems. Europe is an example of ground zero.

**Chris Dall:** [00:21:52] Mike, last week on the podcast, you talked about the U.S. being in a bit of a stay tuned moment in terms of where things were headed. As I noted in the introduction this week, we finally started to see a nationwide uptick in COVID-19 cases, driven mainly by rising cases in the Northeast. We've also had what appears to be a superspreading event in Washington, D.C. and the city of Philadelphia earlier this week reinstated an indoor mask mandate in response to rising cases. Have you seen anything in the past week that gives you a better sense of where this is headed and is what we're seeing an example of what living with COVID will look like?

**Michael Osterholm:** [00:22:27] As we're seeing and have seen throughout the entire pandemic, trends are often not uniform across the states. The one exception to that, of course, was what we saw with Omicron, where there unlike what we saw with Alpha and Delta, which had much more regional patterns to them, Omicron was a viral blizzard during the months of December and January throughout the entire country. So talking about what's going to happen moving forward, it's a question. Overall, the US has seen an 8% increase in cases over the last 14 days, now averaging just over 31,500 cases per day as of Tuesday. And nearly all or 86% of these cases are BA.2. 26 states and Washington, D.C. have seen an increase in COVID-19 cases in the past two weeks. Remember that last week overall, we were still seeing a 6% decrease in US cases compared to two weeks prior, with 21 states and Washington, D.C. seeing increases. As of Tuesday, 21 states and D.C. had an over 20% increase in cases in the last 14 days. However, we're still talking about very low absolute numbers of cases. Just nine states and D.C. are seeing more than 15 cases per 100,000. Rhode Island is seeing the highest number of cases, averaging 32 cases per 100,000. So while we're seeing an increase in case numbers, they are still very low. And let me add one caveat to these case numbers. I will acknowledge I don't know what current case numbers really mean with regard to testing and reporting, but as we see more and more testing shut down, lack of access to testing for many, people now using home testing without



then reporting the results to public health. We have to be very careful about concluding what some of these numbers mean, at least in terms of total cases. Now let's talk about hospitalizations. This week, hospitalizations in the US are still declining and are 15% lower than two weeks ago, sitting at a daily average of just below 15,000. And 24% fewer people are in ICUs compared to two weeks ago. Now we recognize these are lagging indicators, so we have to be mindful of that and knowing that they don't tell us what's happening this week. They tell us about transmission up to several weeks ago. Right now, only 11 of the states seeing an increase in cases are also seeing an increase in hospitalizations. It's important to note that even though some states are seeing high percent increases in hospitalizations, the absolute numbers are still low. For example, Vermont has seen 125% increase in hospitalizations over the last two weeks, but this is equivalent to an average of about five additional cases per 100,000. When cases and hospitalizations are low, an increase of even one or two cases or hospitalizations per 100,000, it can be a huge relative increase. The deaths are also down 26% over two weeks, with a daily average of 530 deaths. According to The Washington Post, eight states have seen increases in their seven day rolling average of daily deaths per 100,000 residents. Maine has seen an 800% increase in their average daily deaths over the past week. But it still is at only 0.67 deaths per 100,000. Colorado has seen a 200% increase in their daily deaths average compared to last week, but it's just at 0.1 deaths per 100,000. Tennessee has seen 143% increase in their daily death average compared to last week, and it is at 0.75 deaths per 100,000. On Tuesday, the daily average number of tests that were done was just over 830,000, up 10% from two weeks ago. However, as I just noted and as you discussed last week, the number of tests being performed is becoming less meaningful due to the decreasing availability and accessibility of testing, as well as the use of at home tests that go unreported. I will touch on this issue in more detail later in the episode, but as I have stated and I believe case numbers are becoming an increasingly unreliable means of surveillance in the US. Surveillance is an important tool to be able to prepare for what is coming rather than react as just another wave hits us. We should be shifting to use hospitalization data as our surveillance instead. But hospitalization data is a lagging indicator of a surge. In short, we don't have any ideal measure right now that is timely, that is sensitive, and that gives us a real sense of where the future is going to play out with regard to this virus. As we move forward in this pandemic, it's going to be important to look at things on a state by state and even a region by region basis. Much of the COVID news in the last week is coming from the Northeast. We have to mention that the outbreak from the

Gridiron Club and Foundation dinner in Washington, D.C., which 700 vaccinated people attended. At least 72 attendees, many of whom are high profile individuals such as members of Congress and journalists, have tested positive for COVID-19, and so far, none of the cases have been reported to be severe. This was the first Gridiron dinner since the beginning of the pandemic, and the president was not in attendance, but several people close to him were. He continues to test negative by all public reports. Washington, D.C. has seen a 76% increase in cases over the past two weeks, with a daily average of 144 cases or 20 per 100,000. Many colleges and universities in the D.C. area have announced they are reinstating their mask mandates. This includes Georgetown, American and George Washington Universities. Johns Hopkins has made a similar announcement as well. And as many of you have heard, Philadelphia is the first big city to announce that their indoor mask mandate will go into effect again this Monday. As I have emphasized so many episodes in the past, we need to have humility. We are still in a stay tuned moment. I think we have to be very cautious to conclude that the United States as a whole will see a specific pattern of illness associated with the BA.2. Only time will tell.

**Chris Dall:** [00:28:56] We've talked a lot in recent weeks about the case for a fourth shot of COVID-19 vaccines. And last week there was some new data published on the efficacy of a fourth dose of the Pfizer vaccine in Israel. Mike, what did those data tell us?

**Michael Osterholm:** [00:29:10] A study published last week in the New England Journal of Medicine described the protection offered by a second booster or fourth dose of the Pfizer vaccine in Israel during the time that the Omicron variant was dominant in the country. The researchers collect data in over one and a quarter million Israelis, who are at least 60 years of age and eligible for the fourth dose of Pfizer vaccine. They compared rates of infection and severe disease between people who had a fourth dose of vaccine at least eight days prior to people who received only three doses or one booster, finding that the rate of both infection and severe disease was lower among people who received their fourth dose. In terms of severe disease, it was three times lower among those who had received a fourth dose, compared to people who had only received three doses. Importantly, this protection did not wane over the six weeks of the study. Of course, we need more information about what it's like three months, four months after the study. In terms of infection, at least four weeks post-vaccination the

rate of infection was two times lower among people who got the fourth dose of vaccine compared to those who had only three doses. But this protection seemed to wane in later weeks, nearing no benefit against infection at eight weeks. The senior author of the study reported that they also saw somewhere between a two-fold and a four-fold protection against death, with the fourth dose compared to only three doses. These data suggests that there is at least a short term benefit to a fourth dose of vaccine in terms of protection against death, severe disease and to a lesser extent, infection. This study had some limitations in that they only presented data for up to two months after the fourth dose. And we'll need to wait to see what kind of longer term protection individuals receiving a second booster dose compared to those who received only one booster dose. The study also only looked at individuals over the age of 60, and it's not clear what impact the second booster would have in younger populations. And finally, the ones who have received four doses of vaccine may have been more motivated to actually not only seek out the vaccine, but to also be certain that they take other measures to reduce their risk of transmission to them or from them to others. And so we'll have to wait and see again what these data all mean in the weeks and months ahead. So what does this study mean? It tells us that we'll need to continue to assess whether boosters that protect for just weeks or months are prudent or justified in the long run. It's clearly not a sustainable approach, and it will be impossible to vaccinate the globe in this way. This provides further evidence we are in need of better vaccines that last longer and are more broadly protective, offering protection against different variants and even recombinant viruses that will likely emerge over time.

**Chris Dall:** [00:32:05] Also, the FDA Vaccines and Related Biological Products Advisory Committee met last week to discuss the booster dose strategy going forward. The meeting seemed to raise more questions than answers about what that strategy will actually look like. What was your takeaway from that meeting, Mike?

**Michael Osterholm:** [00:32:23] Well Chris, the VRBPAC meeting was certainly full of discussion around the issue of the booster dose strategy going forward, and it also included discussions related to how do we update current vaccines to better match circulating strains and how to go about the process now and in the future. The VRBPAC meeting highlighted the fact that these issues are complex and there are a lot of unanswered questions regarding how vaccines should best be used and how should they be updated in the future. As a reminder, additional doses of COVID-19 vaccine

may be needed for two primary reasons. First, either a change in the virus that makes vaccines less effective, as we've seen with the development of new variants of concern or second waning immunity, a decrease over time in the immune system's ability to protect against infection or severe disease when exposed to a virus. The reality is that viral evolution and waning immunity are happening in tandem, which is one of the many challenges making it very difficult to disentangle and identify the best vaccination strategy moving forward. Peter Marks, the director for the Center for Biologics Evaluation and Research or CBER, at the FDA acknowledged at the VRBPAC meeting that the most recent fourth dose second booster recommendation for those over age 50 is really a stopgap measure to protect those at highest risk until there is a better approach in place for moving forward with a booster strategy. There were four major questions raised in this meeting that I want to address. One of these questions is what is the goal of vaccination? We need to better define what the goal is for the booster strategy going forward. What is our goal? Protection against death, severe disease, infection, transmission. What? Depending on what we decide that goal is, the recommendation for additional doses and timing of those doses will surely vary. Another question that was highlighted was, How do we ensure that our vaccines are aligned with circulating variants, given that COVID will continue to evolve? It's quite challenging to predict how often we might see a variant like Omicron that was better at evading immune protection compared to previous variants like Delta that our vaccines work relatively well against. Dr. Trevor Bedford, one of the real leaders in viral genetics related to this pandemic, presented at the VRBPAC meeting, an estimate that showed it's unclear how often we could expect an Omicron like event to happen, ranging from every 1.5 years to every decade. That's one of the challenges in determining whether a new Omicron specific vaccine would be beneficial in the long run, and a reason why vaccines with a broad breadth of protection will be essential. Do we try to match the vaccines to circulating variants? For example, should the current vaccines be updated to protect against Omicron? And would it be less effective if another variant emerged from the original ancestral strain that we saw emerge out of Wuhan in 2019? Or would it still offer a good level of protection? A third question that was brought up is, How do we know when to pull the trigger on distributing new vaccines? One of the things we need is new and better ways to predict how a vaccine will perform against new variants so that the new vaccines can be distributed quickly without an extended process of clinical trials. This can be done through measuring correlates of protection, such as antibodies or T cells in the blood of vaccine recipients. The problem is we don't have good

correlates of protection yet well defined. And finally, how do we manufacture and distribute additional doses in a timely way, whether they be vaccines that are considered a new primary series against a new variant or additional booster doses. If the plan is to make new vaccines available against the new strains of the virus, these vaccines need to be manufactured and distributed to the public, otherwise they are simply pointless. From the VRBPAC meeting, it's clear that we need vaccines that offer high levels of protection against circulating strains, protecting at least against severe disease and ideally against infection too, and that have longer duration of protection that can be manufactured and distributed rapidly. But getting there will be complicated. Next week, we will cover on this podcast discussions around the new information emerging with regard to the success of the adenovirus vaccine or as we know in the United States, the J&J vaccine. I think you will be surprised to learn that the new information coming forward actually raises the potential for this vaccine in the long run to be one of the most critical vaccines we have.

**Chris Dall:** [00:37:11] That brings us to this week's COVID query, which is from Desiree, and it regards the use of rapid home tests. She wrote, "As we are in an environment where local and state governments have dropped mask requirements and at the same time have shut down testing facilities and even changed how they report COVID illness, which potentially changes the data I use to judge severity of COVID in an area, how should we look at home rapid testing?" And so, Mike, I think there are a few questions here in Desiree's query. One is how reliable are rapid home tests for the test and treat phase that we're in right now? But the other, I think, is that if more and more people use the rapid home tests and don't report the results or get PCR confirmation, then aren't hospital numbers which as you noted, are a lagging indicator, aren't they going to become the only metric we have to indicate surges?

**Michael Osterholm:** [00:38:01] Well, first of all, Desiree, thank you for your very thoughtful question. You've raised a number of important issues that Chris is just very nicely detailed. Let me take a stab at this and see what it is that I can add to the overall issue. First, let me talk about the accuracy of these tests. A preprint study that was released on March 2nd looked at the effectiveness of rapid antigen tests by testing over 5,000 patients using PCR and antigen tests every 48 hours for 15 days. The study took place over the span of several months, allowing researchers to get data on the accuracy of these tests for both Delta and Omicron variants. They found that overall, only 24% of

people who were PCR positive tested positive the same day as a rapid antigen test. Let me say that again. Only 24% of the people who were PCR positive, tested positive the same day on a rapid antigen test. 55% tested positive on the antigen test within 48 hours of their positive PCR. A higher percentage tested positive 96 hours after and an even higher percentage one week after the initial positive PCR test. Greater percentage of positive tests reported for those who had multiple consecutive positive PCR tests. In this study, a positive antigen test appeared to be associated with the level of virus. 39% of the people in the study who had at least one positive PCR test never tested positive on a rapid antigen test. But this mostly occurred in individuals higher cycle threshold values, meaning that these individuals had a lower viral load. I'll remind everybody that a cycle threshold is a step where the viral genetics are amplified so that the more times you have to go through amplification, it means the less virus was there originally. So a very high cycle threshold means you had very little virus genetic activity there, whereas if you have a very low one, you actually had a higher level of virus present. When we look at those individuals with a moderate cycle threshold between 25 and 30, only two thirds tested positive with an antigen test the same day. For those with cycle threshold values above 30, only 18% tested positive with an antigen on that same day. What we don't know is the correlation between threshold level and actually the ability to transmit the virus. We make the assumption when there's more virus there, you're more infectious, when there's less virus there you're not. But we still have a challenge, really trying to understand that direct relationship. Let me just say that the study I just referred to is not the first study with findings that suggest that these tests are accurate in detecting the virus in patients with high virus loads, but inaccurate for those with lower viral loads. A study published in November in Nature found that for cycle threshold values 25 or below, again higher levels of virus likely there, rapid antigen test had a sensitivity of nearly 100%. This sensitivity dropped to 76% for cycle threshold values, ranging from 26 to 30, the intermediate level and 38% for cycle threshold values ranging from 31 to 35. Though this study was conducted pre-Omicron, the preprint I just mentioned earlier found no statistically significant difference in test sensitivity for the Delta Omicron variants, so we could expect to see similar sensitivities today. Many are eager to assume that because these tests are picking up cases with high viral loads, they are good enough to be used in place of PCR testing. The reason is that these tests are fairly sensitive to patients with cycle threshold values below 30 that they will be able to detect anyone who is infectious or in need of treatment. This is just not the case. While many studies treat a cycle threshold value below 30 as the benchmark for not

being infectious, there is no extensive data to back this up. And most of the data that does exist was from early in the pandemic, before Delta and Omicron. There is a very likely lower chance of being infectious with a viral load that is low. But we cannot definitively say the sum of the CT value of 30 is not infectious. This makes the inability of these tests to detect this level of viral load very concerning. Further, the sensitivity of these tests begins to decline even before the cycle threshold value of 30. Again, one third of the participants in the preprint study I mentioned that had positive PCR tests with CT values between 25 and 30 did not have a positive rapid antigen test the same day. This occurred for 20% of the patients with these cycle threshold values in the study that was published in November. If these patients had only taken a rapid antigen test, they would have no idea that they were positive for COVID. And though there is some improvement in rapid test performance a few days into the infection, this is not when most patients are testing. They are testing at the onset of symptoms or following a close contact so they can determine if they need to isolate or if they need treatment. And these tests may fail to provide them the information they need to make the right decisions. Studies on the relationship between viral load and disease severity have largely been inconclusive, but we do know that patients with cycle threshold values of above 25 can certainly develop severe disease and die from COVID. A false negative from a rapid test that discourages a patient from getting treatment could be deadly. Even in patients who take an additional rapid test 48 hours after initial test, when test sensitivity is higher, there is still the issue of treatment being delayed. COVID treatments need to be administered early in the infection, and so any delay in treatment, including those resulting from an initial false negative test, could increase the patient's risk of developing severe disease and dying from COVID. This is not to say that these tests should be disregarded completely. As we covered last week and in other previous episodes, there are many equity issues and other systemic barriers that can prevent patients from accessing a PCR test. For those that are unable to access a PCR test, these antigen tests are certainly better than nothing. But we should not be taking away PCR testing resources, thinking that these tests are an adequate replacement. In addition to the impact that this has on patients ability to know when to isolate and get treatment, there's another major issue that results from this lack of PCR testing and increasing reliance on at home rapid tests, inadequate disease surveillance. Many individuals that test positive using a rapid antigen test do not get the results confirmed using a PCR test. This means that their case will go unreported and not included in the rates of daily cases we use to assess the state of the pandemic. As we shift more and

more towards the use of these rapid tests, this underreporting issue will only worsen and daily cases will no longer be an accurate way to assess the level of transmission in a given community, a point that I've been hitting home throughout this entire podcast. As I mentioned earlier, this is causing us to shift towards using hospitalization data as our means of surveillance. As I've also said, the problem with this, of course, is that hospitalization is a lagging indicator. Today's hospitalization numbers are not reflective of today's transmission levels. They're a reflection of the level of transmission days to weeks ago. This means that public health decisions made in response to a rise in hospitalizations will go into effect a few weeks after they are really needed, forcing us into a reactive public health strategy rather than a proactive one. Finally, testing whether it be with rapid antigen tests or PCR tests is not a foolproof prevention strategy. The use of rapid and PCR testing before large gatherings, travel, visiting high risk family members or even routinely used in some schools and workplaces which became increasingly popular in the Omicron surge, does not mean that you will reduce transmission. As the studies we discussed earlier demonstrated, a test is only an indicator of whether or not someone has COVID at a point in time. It does not mean that they won't test positive again in 24 hours, and their negative test in that moment, particularly with a rapid test, does not even mean that they are not infectious at the time the test was taken. We saw perfect example of this last November at a holiday party in Oslo, Norway, where guests were asked to take a rapid antigen or PCR test 1 to 2 days before the event. All those in attendance tested negative before the event, yet the event was still a super spreader situation, with 59% of party guests infected with the virus. Testing did not prevent transmission here. Though this is especially true in the case of less accurate rapid antigen tests, it is also the case with PCR tests. No matter how accurate a test is, it is not a substitute for primary prevention. So what is the bottom line? Desiree, you wanted to know. Yes, rapid antigen tests are far less sensitive than PCR tests. And though they are good at detecting the virus and patients with high viral load, they can still produce false negative results in patients that are infectious and at risk for severe disease. They may be better than nothing, but they are not an adequate replacement for PCR tests, especially as we are implementing a test and treat strategy. We cannot effectively test and treat if we cannot provide the population with timely and accurate tests. If we continue to make PCR testing less accessible for more of the population, we will likely see even fewer patients getting treated for COVID in a timely manner. More reliance on lagging indicators to determine the level of transmission in



the community, and even more feelings of false security as people promote the use of these tests as a strategy for preventing COVID related illness.

**Chris Dall:** [00:48:29] Mike, what can you tell us about our latest beautiful place submission?

**Michael Osterholm:** [00:48:34] Well, again, Chris, I love this beautiful place section. It allows us to express, I think, those wonderful good aspects of life right now. And this is surely one of those. This is actually from Shelby. And Shelby wrote, "Dr. Osterholm, an amazing team at CIDRAP. I have to start by saying that I'm so grateful for this podcast. You're straight talk about the pandemic's helped me make decisions about how to safely live my life on a daily basis, and I really can't thank you all enough for that. My beautiful place is my neighborhood, Uptown in the great city of Chicago. Before the pandemic, I was a touring theater technician that went around the world stage managing plays and musicals. I sincerely miss visiting new places and learning about new cultures, so I decided to fill that gap by visiting every street within a two mile radius of my apartment. I look at a map and deduced that there were about 140 streets to visit, so I would have plenty of places to check out whenever I took one of those oh so necessary mental health walks. This quickly turned into a passion project of mine as I started to take all the public art, historic architecture and nature and our gorgeous parks. I've seen everything from the shores of Lake Michigan to the iconic Wrigley Field and even discovered a few historic landmarks tucked away in residential areas. I've been meeting my neighbors as I pass them each day and learning about local politics and events through stickers and fliers. In visiting all these streets, I've fallen in love with this beautiful place, my very own neighborhood, that I didn't really have time to explore before the pandemic. And I've developed roots here, and I've fostered a sense of community at a time when it's more crucial than ever to surround yourself with friendly neighbors and amazing sites. I've attached some pictures from a few of my walks over the last year. I only have five streets left on my list, but I definitely won't stop taking walks around my beautiful neighborhood any time soon. Thanks, Shelby." Well, please go to the website. Take a look at Shelby's pictures. They really are wonderful. And, you know, it's one of the, I think, the truisms of life and reflected here in Shelby's wonderful comments, sometimes some of the greatest beauty in life is right there in our world, and we don't understand or take the time to realize that. So I hope that every one of us learns from this beautiful place and helping to remind us we can find beauty in so many

places in life if we just take the time to look. And in a world of COVID, in a world that is so challenged today with so many other issues, taking time to find the beauty in our own lives is a lesson that I know I need to continue to remind myself of just how important that is. And I hope all of you, like Shelby has done, can find that beauty in your own lives, where before it wasn't truly appreciated.

**Chris Dall:** [00:51:35] Mike, what are your take home messages for today?

**Michael Osterholm:** [00:51:40] Well, let me just start out by saying that I wouldn't call this a take home message, but, gosh, it's good to be back with so many people again. And each week, this is kind of an anonymous event where Chris and I work together to do this podcast with the podcast team, which I work with the most amazing team to help prepare the information that you receive every week. And it's only because you do give us the feedback and you do respond and you do tell the stories about what being part of this podcast has meant to you and what it means for others. And I just have to come back from time to time and say two very, very important words. Thank you. It is so wonderful to have this relationship. It's not just a one way broadcast. It goes both ways. And I can't tell you how much your words mean back to us. So thank you. I, I feel like we get the better end of the deal every week. The points that I would emphasize today is that I just have to again say I don't know what is going to happen with COVID in the United States. If ever a time for humility, it's now. Will it be like we've seen in the United Kingdom with increasing BA.2 causing major surges in cases and even hospitalizations? Is that what's going to happen in the Northeast? Will it happen in other areas or will in fact be like other parts of Europe where we've actually seen very limited increases in cases due to increasing BA.2 activity? Go to Indonesia, same thing, major increase in BA.2 activity, very limited increase in cases. So I don't know what's going to happen. We have to be prepared for any and all possibilities. Next is that testing as we know it is going to become more difficult to find if you're looking for a PCR test. That is unfortunate because that has been the framework upon which we've looked at trying to understand the epidemiology of this infection in our communities. Rapid antigen testing is better than nothing, but as I just shared with you, there are limitations there. And most importantly, it's not going to get reported in most instances. That leaves us, I think, vulnerable to understanding what's happening in our communities. And finally, I think we really need to ask ourselves the critical questions regarding the use of COVID vaccines, what they can do to protect us against variants and recombinant viruses, and what can

they do with waning immunity? We don't know. We have so much to learn. Don't get me wrong, these have been remarkable tools, these vaccines. They have saved millions of lives. But we now know with certainty that they can't be the final product. We need new and even improved COVID related vaccines, and this has to be a priority. So in the meantime, hang on, use the tools we have and hopefully time will provide us with even more effective vaccines that can deal with variants that can deal with waning immunity. But for now, this is what we have and we have to deal with our response based on that issue.

**Chris Dall:** [00:54:56] And do you have a closing song for us today?

**Michael Osterholm:** [00:55:00] I do. And it's one that actually I've had for a number of weeks and just have not used it before. And it was because I wanted the right moment. I wanted a time when I think that we might need this song as much as we appreciate it. We're at a time right now where we need to understand the uncertainty that's taking place in our lives with regard to COVID. That's taking place with the economy, taking place with Ukraine and all the other challenging spots in the world. We need to also take care of ourselves in a way that says there is still good, there's still light, there is still a reason to search out the good in the world. And so this song actually, believe it or not, was originally composed by Charlie Chaplin, as the music goes. And the words were written by John Turner and Jeffrey Parsons. All of it occurring in 1954. The late Nat King Cole recorded this in 1954. It reached the number ten on the Billboard charts and number two on the U.K. singles. This is a song that has been done by a number of other groups since that time, including Natalie Cole, late Nat King Cole's daughter, who, too, unfortunately, is no longer with us. This was a song about a singer telling the listener to cheer up. And if there is a bright tomorrow, just as long as they smile. Here today, "Smile." Nat King Cole. "Smile, though your heart is aching. Smile, even though it's breaking. When there are clouds in the sky, you'll get by if you smile. Through your fear and sorrow. Smile. And maybe tomorrow you'll see the sun come shining through for you. Light up your face with gladness. Hide every trace of sadness. Although a tear may be ever so near. That's the time you must keep on trying. Smile. What's the use of crying? You'll find that life is still worthwhile. If you just smile. That's the time. You must keep on trying. Smile. What's the use of crying? You'll find that life is still worthwhile if you just smile." Thank you, Charlie Chaplin, John Turner, Jeffrey Parsons, and, of course, the late Nat King Cole. Smile. Just remember that. Well, thank you all so very

much for being with us again for another week. I hope the information is helpful to you. We already are in the works for next week's podcast. Looking at some of the issues, I talked about the new variants, BA.4, BA.5. We're going to be talking about the adenovirus vaccines and what they mean in terms of potential future use and protection. And we will share with you an update on what's happening with cases here in the United States and what we're learning about the emerging epidemiology of BA.2 outside of Europe. So thank you for being with us. I hope you have a safe week. Even where we're starting to see case numbers increasing, take every precaution you need to protect yourself, particularly given your underlying health conditions. I constantly think about those who are more challenged developing immunity with the vaccine, such as the immune compromised. We never forget about you, ever. I also want to emphasize the fact that we don't forget about you with long COVID. I know that you are truly, truly looking for answers that have not been available to date. And so we think about you a lot and what we can do to help with that. And for all of those of you who have companion animals, I hope that you go and when you get done with this, go give them a hug. They need it, but you probably need it even more so. Thank you so much for being with us. Chris, thanks again for another great show and to the podcast team. Be safe. Everyone, be kind. And remember, these cases are not just about us. They're about our grandparents, our parents, our kids, our grandkids. They're about our friends. We all are in this together. Thank you.

**Chris Dall:** [00:59:29] Thanks for listening to this week's episode of the Osterholm update. If you're enjoying the podcast, please subscribe, rate, and review, and be sure to keep up with the latest COVID-19 news by visiting our website [CIDRAP.umn.edu](https://CIDRAP.umn.edu). This podcast is supported in part by you, our listeners. If you would like to donate, please go to [CIDRAP.umn.edu/donate-now](https://CIDRAP.umn.edu/donate-now). The Osterholm update is produced by Sydney Redepenning, Cory Anderson, Angela Ulrich, and Meredith Arpey.