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Expert Interviews

National STD Curriculum Podcast

Mpox Virology: What Do We Know?

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Season 3, Episode 7

Dr. Boghuma Titanji, an Emory University Assistant Professor of Medicine, discusses mpox virology in an interview with the National STD Curriculum Podcast Editor Dr. Meena Ramchandani. This seventh episode of the ongoing mpox series was recorded prior to WHO's November 28, 2022 decision to change to "mpox."

Topics:

- Mpox
- MPX
- hMPX
- Monkeypox

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Transcript

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In this episode:

introduction**[00:00] Introduction**

Hello everyone. My name is Meena Ramchandani. I'm an infectious disease physician at the University of Washington in Seattle. This podcast is dedicated to an STD [sexually transmitted disease] literature review for health care professionals who are interested in remaining up-to-date on the diagnosis, management, and prevention of STDs.

This is the seventh episode of our monkeypox podcast series, which focuses on the 2022 outbreak. In this episode, we will discuss the virology of monkeypox virus infection. The sixth and seventh episodes are from an interview with Dr. Boghuma Titanji recorded in November of 2022. In the last episode, Dr. Titanji and I discussed inequities and international aspects of monkeypox virus infection. Dr. Titanji is an assistant professor of medicine in the Division of Infectious Diseases at Emory University in Atlanta, Georgia.

evolution-outbreak**[00:55] Evolution of Outbreak**

Dr. Ramchandani
So, we've heard a little bit about hMPX epidemiology, transmission, and clinical presentation in some of our recent previous episodes. Can you tell us a little bit more about the virus origin in the 2022 outbreak and how does this compare to previous outbreaks both in the U.S. as well as in other countries?

Dr. Titanji
Right. The outbreak in 2022 is actually caused by Clade II of the virus, which is the clade of the virus that primarily circulates in West Africa, and it's also the clade of the virus that caused the biggest outbreak in Nigeria, which happened between 2017 and 2018. And the initial signal that kind of led to the ongoing outbreaks being identified was that they were noticing individuals in the United Kingdom presenting with monkeypox and getting diagnosed with it without any history of having traveled to a country that is endemic for monkeypox. And as the cases kept coming in, they noticed that these cases were primarily clustering in gay, bisexual, MSM, and in individuals who were connected through their social networks. And the same patterns kind of emerged around Europe, kind of tracking very closely with large Pride events that happened in Spain, in the Netherlands, and in Belgium. And that really led to the epidemiological signal alerting the world that there was this outbreak.

When you look at the sequences of monkeypox that have been isolated or the initial sequences that were isolated in the outbreaks that were happening across Europe, there's actually a study that was published very early on by researchers in Portugal. That showed that the sequences isolated for monkeypox patients in Portugal clustered quite closely with the sequences of the virus that had been isolated during the Nigeria outbreak in 2017 and 2018. So there is a certain degree or certain group of thought that thinks that monkeypox transmission probably was happening at a low level and had gone unnoticed for some time before an amplification event likely around Pride events across Europe that led to a much bigger signal and it being recognized as an outbreak. So, what we are seeing right now may actually be an extensional continuation of an outbreak that started in Nigeria in 2017, 2018.

And another aspect or another piece of the puzzle in terms of the virology of the virus that's circulating now is normally orthopoxviruses tend to evolve very slowly. They're not like the virus that causes COVID-19. They're not RNA viruses. They're a lot better at editing their DNA when they replicate, so they don't make a lot of errors in the replication. And so, they introduce errors in their replication about one or two single nucleotide polymorphisms per year. However, when you compare the sequences that were obtained during the Nigeria outbreak and the sequences that were obtained during the outbreaks ongoing currently, over the course of five years, the virus has accumulated about 50 single nucleotide polymorphisms, which is a lot more than one would expect over that time period for an orthopoxvirus, suggesting that it is evolving a lot quicker.

And when you look at the signature of these changes, they suggest that those changes have occurred under the pressure of a DNA editing enzyme known as APOBEC [apolipoprotein B mRNA editing catalytic polypeptide-like], which is a human DNA editing enzyme, suggesting that transmission has been occurring in

humans since 2017 to a certain degree that has led to the changes in the genome. And those single nucleotide polymorphisms accumulating a lot at a higher rate than one would expect. So these are some of the clues that are making phylogeneticists and evolutionary virologists think that what we're seeing now is actually a continuation of an outbreak that started in 2017. Now in terms of these differences, we don't know what these changes mean. Because the question I get often is, are these mutations then making the virus more virulent, or does it account for the virus transmitting in the ways in which we are seeing now? We know that there are changes in the genetic constitution of the virus in the nucleotide sequence, but we don't know what these mutations mean, and we know that they have occurred under the pressure of APOBEC, which is a human DNA editing enzyme.

Dr. Ramchandani
So we don't have any evidence that this might be due to the biological features of the virus that have changed those previous years. But there are mutations that do show that the strain has changed or evolved.

Dr. Titanji
Yes, absolutely, and I think that that is an area that a lot of people, a lot of groups are looking at is now going and looking at those gene mutations and trying to understand what they actually mean in terms of the phenotype that they confer. You know, does it mean that it makes it more easy for the virus to transmit through mucosal route or some of the new modes of transmission that we are seeing now? These are areas of active inquiry that we need to get a better sense of.

clade-i-vs-clade-ii-virulence**[06:50] Clade I vs Clade II Virulence**

Dr. Ramchandani
Now, this is a less virulent clade, correct? Of the virus that is causing the 2022 outbreak?

Dr. Titanji
Yes, absolutely. The Clade II of the virus is a lot less virulent than Clade I. Clade I tends to cause an infection that is more similar in phenotype and can even be almost indistinguishable in clinical manifestations to smallpox, and Clade I tends to cause a much milder syndrome. And when you look at historical cohorts reported from the DRC [Democratic Republic of Congo] and other African countries, the estimated mortality rate for Clade I, which is the more virulent virus, is about 10%. Whereas for Clade II, it hovers around 1%, and in the current outbreaks, it's about 0.03% mortality. So actually quite a difference in virulence between the two clades of the virus.

Dr. Ramchandani
Thank you, and do we have any evidence about what could account for the differences in virulence between the different strains?

Dr. Titanji
It has been hypothesized that there might actually be specific virulence-associated genetic differences between the two different clades of the virus. Actually, Clade I and Clade II are 99.4% similar to each other. And so quite closely similar viruses, *but* there are some differences in their genome. It is hypothesized that some of these differences may actually be reflected or may actually correspond to specific virulence factors that account for the clinical manifestations being so different for Clade II compared to Clade I. But, again, monkeypox is one of those viruses that had been pretty significantly understudied compared to, say, other orthopoxviruses like smallpox or vaccinia virus. So, this is again another area of active inquiry, and we need to gain more understanding on why the virulence is so different between the two clades, but also why Clade II is behaving the way it's behaving in the ongoing outbreaks.

different-symptoms**[09:08] Different Symptoms**

Dr. Ramchandani
And so, in the ongoing outbreak with Clade II, we have some patients who are presenting with, let's say, a

single genital ulcer. And then there's some patients, more rarely, who have severe clinical presentations, they might get sepsis, encephalitis, or it can affect the lung or the heart. Does this maybe have to do with the virus, the viral strain, the host, or possibly both? Can you tell us a little bit more about if we have any evidence for this?

Dr. Titanji
I think that it's likely a combination of both. I think I would start with the host factors. We know now from a growing amount of clinical evidence that there is quite a strong association between people who have a diagnosis of human monkeypox and association with having an existing diagnosis of HIV. And that people with HIV not on antiretroviral therapy and who have low CD4 counts and basically are in clinical AIDS have more severe manifestations of monkeypox. We also know that the B cell response, the T cell responses are very, very important for clearing orthopoxviruses, including monkeypox. So, in individuals who are severely immunocompromised, it's not entirely surprising that they're not able to effectively clear the virus and, as a result, are presenting with more disseminated features of the infection and also presenting with more complications.

Actually, of the deaths that have been reported globally in the current outbreak, I think, at last count, there had been 38 deaths recorded. A lot of these deaths have happened in individuals with underlying immunocompromised, be it as a result of having HIV and not being treated for their HIV or other individuals who are on chemotherapy or have another reason for having an immunocompromised immune system. Now coming back to, sort of like, the viral factors that may also be explaining, I think that it's also pretty clear that inoculum matters enough. So a lot how much virus is introduced and where it's introduced.

Dr. Ramchandani
And how it's introduced, right?

Dr. Titanji
And how it's introduced, exactly. There is a very compelling case series that was published out of Spain, I think in the *Lancet,* that did show quite a very strong correlation: Individuals who presented with oral and pharyngeal lesions were individuals who were also admitting to having oral sex as their primary mode of exposure. And those who presented with penile and anal lesions were those who reported having insertive anal sex or receptive anal sex. So really tracking with the point of inoculation. And there've now also been case reports of health workers who have been exposed to monkeypox through needlestick injury developing lesions locally at the point of injury. And that really again tells you that the clinical manifestations track quite closely with where the virus is introduced, but also track quite closely with how much virus is introduced, you know, so we're seeing a bit of a reflection of that.

In terms of whether we've actually seen a change in virulence that may be pointing in the direction of the virus itself is more virulent, we don't really have a strong indicator for that. Because if anything, the mortality rates in the ongoing outbreaks have been much, much lower than what has been reported previously in West and Central Africa when these outbreaks have happened in these settings. But I would add the caveat that there is a bit of a confounding factor here, like what people don't realize is the mortality for the Clade I virus that we're seeing right now, which is so incredibly low in the U.S. at 0.03% or whatever that is, could really still be 1% in Cameroon or Nigeria. Because, again, oftentimes, these outbreaks are happening in very remote parts of these countries where there isn't enough access to medical care, and patients may be succumbing to bacterial sepsis just from having bacterial superinfection of skin lesions or just the lack of basic medical attention that would treat complications for which they would not die if they were in a city or in a Western hospital where you had access to a lot of treatments, et cetera. So, that may be playing a role in some of the differences that we are seeing. I don't think that this is strong, compelling evidence that makes me think that there are new mutations in the virus that has made it meaner. That's not to say that it could not change because viruses evolve. That's what viruses do. And one cannot predict if, in 10 years, if monkeypox keeps circulating in the human population, will we see a difference in virulence? I cannot read the tea leaves on any virus, I'm afraid.

Dr. Ramchandani
It is the nature of viruses to continue to survive within its host environments, and so I guess it's our job to try to prevent that from happening as much as we can.

hiv-mpox-tecovirimat**[14:47] HIV, Mpox, and Tecovirimat**

Dr. Ramchandani
I do want to ask you this one question: When we're thinking about virology, what's the most common question you get about hMPX virology, and how do you usually answer this question?

Dr. Titanji
I'll probably split it in two: the most common question I get from patients and the most common question I get from my colleagues. So, from my patients, I get the question of, is this going to persist and be like HIV? Because unfortunately, you know, there's that strong association between having a diagnosis of HIV and presenting with monkeypox, and about 60% of our patients in Atlanta have been people with HIV. So a lot of the people I've treated with human monkeypox have had that fear that they had acquired another virus that would be with them forever, and they're already living with HIV, so this kind of brings back flashbacks of their initial diagnosis with HIV and being told that it's a virus that we could not cure and we still can't cure, although we can control. So, to that group of individuals, and for that question, I think I'm usually very quick in providing reassurance that, fortunately, for a lot of people, monkeypox is a self-limiting infection, and a lot of people recover fully. The recovery process can take two to four weeks. But for most patients, in 99% of cases, a lot of people would make a full recovery. And for individuals who have not come in contact with human monkeypox, I encourage them to get vaccinated because that would protect them from, or at least reduce their risk of getting an infection or lead to milder symptoms if they indeed come in contact with monkeypox. And for those who are not taking their ARTs, I encourage them to take their ARTs because, again, an intact immune system is one of those things that you want to shore up to make sure that if you do come in contact with human monkeypox, it is indeed a self-limiting infection for you.

Going to the other side and thinking about the questions that I most frequently get from my colleagues is, and I've gotten that twice this week, it's how long can I give someone tecovirimat?

Dr. Ramchandani
It does come up.

Dr. Titanji
Yes, that has come up.

Dr. Ramchandani
Can I give it again? A longer course or another course?

Dr. Titanji
Yes. And I think that the reason why that's coming up is as the case numbers have gone down, the cases that a lot of clinicians are dealing with right now are the more challenging cases of human monkeypox that's happening in individuals, unfortunately, with significant immunocompromise. And in these individuals, they tend, without an immune system, without T cells, without the ability to make antibodies, you're not going to clear the virus. So, a lot of clinicians are experiencing putting people on 14-day course of tecovirimat, stopping that and promptly seeing the patient, quote-unquote, relapse with new lesions popping up, et cetera, and they're kind of struggling with how to navigate that. So, the way in which I usually respond to that question is, first of all, the 14-day treatment course is entirely based on animal models for monkeypox, and it's also extrapolated from data on the disease course of smallpox.

So it's really, again, showing you the fact that a lot of what we know about monkeypox is extrapolated from other orthopoxviruses. And sometimes, when we extrapolate things like duration of treatment would be sufficient for vaccinia or for smallpox, but maybe for monkeypox, it needs a longer treatment course. So, I

encourage people not to have a very fixed mindset about, oh, it says on the package insert 14 days, because it's not based on a clinical trial done in humans that actually determined that that was the sufficient duration of treatment. That's the first consideration. The second consideration is in individuals who have AIDS and don't have an immune system; when you stop the antiviral that's controlling the monkeypox infection, you will promptly see viral replication resume because they cannot clear the virus without an immune system.

So, I think the field is moving towards considering extending antivirals for these patients until the immune systems recover while they're on antiretroviral therapy in order to give them the ability to have the immune system that allows them to also clear the virus by themselves. And a lot of these decisions can be done or can be made in consultation with the Poxvirus [and Rabies] Branch at the CDC, who are incredibly helpful when you call them up to discuss some of these challenging questions. So that is kind of my take, what I say to my colleagues who ask how long should I be treating this patient with tecovirimat.

tecovirimat-resistance**[20:17] Tecovirimat Resistance**

Dr. Ramchandani
I'd loved to ask you what are your thoughts on the potential concern for resistance to Tecovirimat?

Dr. Titanji
Yes! It is concerning, certainly, because when you look at in vitro studies of monkeypox with the drug, kind of some of the initial studies, the preclinical studies that were done, it doesn't take a lot in vitro to select for tecovirimat resistance. It has a low barrier to monkeypox resistance in vitro. However, there is reassuring data from the CDC, some of the initial sequences that they have been collecting nationwide from some of these challenging cases from patients who have been on tecovirimat for longer than the 14-day duration. They have *not* been able to isolate any cases in which they detected resistance. And this question was posed at the last ID Week meeting on a panel on monkeypox, in which I was participating, to the CDC colleague who was presenting on treatment, and they did say that they have not seen any resistance select for tecovirimat. And I would encourage clinicians who are dealing with these challenging cases and extending the treatment courses of tecovirimat for their patients to reach out to the CDC so that they can send samples. Because I think it's important to monitor sequentially in these individuals if someone's been on tecovirimat for a month, for two months. Maybe we did not detect resistance at one month, but will we detect resistance at month two, et cetera? And, of course, the normal monitoring that happens while patients are on medications, particularly in the case of tecovirimat, monitoring for liver function markers and making sure that those are continuing to remain within normal limits is another important consideration.

Dr. Ramchandani
Thank you so much. This has been so educational for both myself and the audience, and I just want to thank you, Dr. Titanji, for joining us today. It's been an absolute pleasure to speak with you on these very important topics, so thank you for being here.

Dr. Titanji
It was my pleasure, and thanks for inviting me.

credits**[22:30] Credits**

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