



## REVIEW ARTICLE

## Monkey-Pox Virus and It's Impact

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### Introduction and History

Monkey-pox has been one of the most recent outbreak in more than 10 countries worldwide. Monkey-pox is a DNA virus that is an orthopox virus family which is actually related to smallpox, but not as dangerous. So some key differences are that it is a DNA virus and whereas with SARS-CoV-2 which had 30,000 RNA codes basically, the monkey-pox is a double stranded DNA virus and its much larger virus which has 200,000 base pairs, so probably more pairs to sequence and probably more genes to sequence as well. It's probably been infecting humans for a very long time but it was first isolated in 1958 in crab-eating Macaques, which are like monkeys and that's where the name monkey-pox stuck. Now it made it's jump into humans in the Democratic Republic of Congo in the 1970s, that's the central African Republic. It was first discovered in the Democratic Republic of Congo and this is where we see the Central African strain of the monkey-pox virus. Now, there is a West African strain which is present in the other countries in West Africa. The death rates from infection from the Central African strain is 10% whereas the West African strain is 1-3%. And now, we are looking at these viral infections in the UK, United States, they seem to be related to the West African strain. Even though the name monkey-pox has the word monkey in it, it's a misnomer because actually these type of infections come from any small African mammals and rodents and that was highlighted with the recent outbreak about 20 years ago in the United States [1].

Back in January 2004, there was a paper published in The Lancet Infectious Diseases titled Human monkey-pox: an emerging zoonosis which says that human monkey-

pox is a rare viral zoonosis endemic to Central and Western Africa that has recently emerged in the United States. Laboratory diagnosis is important because the virus can cause disease that is clinically indistinguishable from other pox-like illnesses particularly smallpox and chickenpox. Although the natural animal reservoir of the monkey-pox virus is unknown, rodents are the probable source of its introduction into the USA. A clear understanding of the virulence and transmissibility of human monkey-pox has been limited by inconsistencies in epidemiological investigations. Monkey-pox is the most important orthopox virus infection in human beings since the eradication of smallpox in 1970s. There is currently no proven treatment for human monkey-pox and questions about its potential as an agent of bio-terrorism persist [2]. The scientists have been looking at this particular virus for some time and they have understood quite a bit about it.

In the year 2003, there was an outbreak in United States of monkey-pox and this was because of animals that were transported from endemic region of Central Africa and were brought in the United States and caused animal to human infections. So, there was a study done, looking at those of the ones that had medical records, 34 of them researched and they were found in almost every case to have a rash that progressed to a raised lesion that progressed to a pustular lesion and that lasted and crusted over which took about 2-3 weeks to completely go away. These would show up on the trunk of the body, that's the central portion and then goes to the arms and even the palms and soles. There was further investigation done during this time to see just how far this infection had gone and what was interesting is that, they has picked up on 3 individuals



**Citation:** Tahiliani V, Kolotylo T (2022) Monkey-Pox Virus and It's Impact. J Infect Dis Epidemiol 8:273. doi.org/10.23937/2474-3658/1510273

**Accepted:** August 03, 2022; **Published:** August 05, 2022

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that were positive for the antibodies against monkey-pox but never knew that they had symptoms. And what came out was that, they had actually been vaccinated against smallpox, and one of them was 13 years prior and other one was 29 years prior to the infection with the monkey-pox and another individual, 48 years prior was vaccinated with small pox vaccine and that seemed to confer protection against symptomatic monkey-pox disease.

## Symptoms

When looked at the outbreak in 2003 in United States, it was noticed that those that had the monkey-pox virus had Rash- 97% of the time, Fever- 85% of the time, Chills- 71% of the time, Enlarged lymph nodes- 71% of the time, Headaches- 65% of the time and Muscle aches- 56% of the time.

## Transmission

There are 2 ways by which this virus can be transmitted: that is through humans and through animals. And by close contact, touching source, specially if they are open or even touching the clothes that the patient was wearing and picking it up from there. In terms of animals, it is much of the same, so close contact, but also biting and scratching or even eating the meat of those animals.

The incubation period may depend on the mode of transmission, for instance, the incubation period would be shorter in case of something like scratching or biting and it's been said upto 9 days, so for biting and scratching, 9 day incubation period before its actually seen. The touching however can be up to 13 days, or even longer. The R0 (R-nought) for monkey-pox is between 0-1, which means that this outbreak tends to fizzle out, because the person can not always reliably transmit this virus because it's obvious when the person has the virus and it's easy to isolate these patients. Large respiratory droplets have also been implicated in the transmission from human to human of monkey-pox and specifically, its not like it would be with measles or SARS-CoV-2 but for instance, if you are within 6-feet of somebody, you would have to be there for at least 3+ hours to have reliable transmission. This is classically what is being noticed and observed.

What's different now is we are starting to see more and more patients becoming infected and specifically in a population in the UK that is a population of gay and bisexual men [3].

But there is also a report of a Sauna outbreak of monkey-pox in Spain. In Belgium, three cases have been linked to a large-scale fetish festival in Antwerp, according to the organizers. In a article, it reported that, in the UK, a link was first drawn between gay men and monkey-pox earlier in the week, with the UK Health Security Agency (UKHSA) urging gay and bisexual men

to be alert to any new rashes or lesions on their body, including their genitalia [4].

## Treatment

Generally speaking, the treatment for monkey-pox is really supportive care, that means if there is nausea and vomiting, make sure that the patient is well hydrated and doesn't become dehydrated, make sure that the electrolytes are replaced and if this is done, most people recover. There are antiviral treatments: the first one is Tecovirimat 600 mg orally BID for 14 days. This is FDA approved for smallpox in July 2018. So this could be considered off label for monkey-pox but it seems to work very well in both situations and the mechanism of this drug is that it prevents the formation of a very important protein in the virus that makes it infectious and able to infect other cells in the patients. The next antiviral medication is Brincidofovir 200 mg orally weekly times 2 doses. This was FDA approved for smallpox as well in June 2021. The last one is Cidofovir, but the issue with this one is that it's not really approved for smallpox or even monkey-pox, but rather CMV retinitis and the problem with it is that, it can cause problems with the kidneys, in fact there's a black box warning on it.

## Vaccines

Two vaccines have been on the center stage for the last 2 decades: ACAM2000 and JYNNEOS. ACAM2000 was a vaccine that was approved in 2007 and it was at its core a replication-competent vaccinia virus which means that it actually did replicate inside the human cells where the vaccine was given and it caused a "take" (lesion in the area of vaccination), so you knew that the virus had taken hold and it was to create the antibodies that were necessary for the patient who took the vaccine to get appropriate antibodies to protect them from monkey-pox and also smallpox. However, because it was replication-competent, there were risks of inadvertent inoculations and auto-inoculations, there were risks of serious adverse events, particularly myopericarditis in 5.7 per 1,000 primary vaccines. The effectiveness of this was good compared to the one that was prior to this in 2007 which was DRYVAX, that was the standard prior to 2007 which is when ACAM2000 was FDA approved and the way that this was administered was in the skin by multiple puncture techniques in a single dose. In September of 2019, there was approved JYNNEOS, this is also a vaccinia vaccine, specifically it's a Replication-deficient Modified vaccinia Ankara, which means that the vaccine contains a virus that does not replicate and because it does not replicate, that reduces the risk of a lot of the side effects that were seen with ACAM2000. So, there is no "take" after the vaccination, that means there is no lesion in the area where the vaccination was given. There is no risk therefore of inadvertent inoculation and auto-inoculation. They expect there to be fewer adverse serious events with this Replication-

deficient Modified vaccinia Ankara and the cardiac adverse events are believed to be lower than that of the previous vaccine which was the ACAM2000 and the way that this is administered is subcutaneously in 2 doses, 28 days apart [5].

In a FDA approved news release, it was mentioned that how they checked the efficacy of the new non-replicating vaccine JYNNEOS, and because there was already a gold standard vaccine, they weren't going to do a randomized placebo-controlled trial because that would be unethical to give anybody a placebo to see if that was going to work and so what they did was something called a non-inferiority study where they gave half of the participants, the old vaccine and half, the new vaccine and in this case they looked at the immune response in both and they were found to say that the group vaccinated with JYNNEOS had an immune response that was not inferior to the immune response to ACAM2000. They also say that vaccine effectiveness for the prevention of smallpox was also inferred from supportive animal studies that showed that prior vaccination with JYNNEOS protected non-human primates who are exposed to the viruses related to the smallpox virus. The safety of JYNNEOS was assessed in more than 7800 individuals who received at least 1 dose of the vaccine. The most commonly reported side effects were pain, redness, swelling, itching, firmness at the injection site, muscle pain, headache and fatigue. No safety concerns that would require a medication guide have been identified for JYNNEOS. It is administered in two doses given four weeks apart [6].

### Post-Exposure Prophylaxis

First thing that can be done is to get Vaccinia Immunoglobulin and this is what people who are immuno-compromised might need to do. Basically, these are antibodies that are derived from other patients who have had the infection in the past or they are genetically engineered to be antibodies against vaccinia which will cross react and also go against the monkey-pox virus. However, the CDC recommends even up to 14 days post exposure, you can actually take the vaccine, but generally that is for immuno-competent patients.

### Monkey-Pox Mutation Update

By looking at the monkey-pox genomes evaluated in 2021 and 2022, 3 out of the 10 that were analyzed had distinct and different genomes, of course they were all related to each other but at least two separate monkey-pox outbreaks were underway suggesting wider spread [7].

There are two different variants or clades of monkey-pox. There is the more severe Congo Basin variant which has about 10% mortality and there is the west African variant which has about 1% mortality. If we look specifically at the country of Nigeria, they did not see a case of monkey-pox until recently since 1978, and then

all of sudden in 2017 there was a case of an 11 year old who was confirmed to have monkey-pox. Since that time and up until 2022, there have been 500 cases and as the report points out, the thing that was different about these 500 cases is that these were primarily spread through sexual contact with men, essentially gay and bisexual men. During this time, there were cases that were popping up in places like Israel, in the UK and also in Singapore but all of these had connections with people who had travelled from the endemic area of Nigeria in this case. Monkey-pox is a DNA virus and as such DNA viruses, generally with some exceptions, don't mutate as much as RNA viruses. In fact, the mutation rates in this type of a virus is usually 1-2 base pairs per year. When it was looked at the mutation rates from 2017 to 2022 in these Nigerian monkey-pox cases, it skyrocketed to about 47 per year. Furthermore, these did not appear to be random mutations, these were very specific mutations, in fact most of the mutations involved a base pair going from a thymine and cytosine to a thymine and another thymine or the other one was going from a guanine and adenine to a adenine and a adenine [8].

There is a very specific innate immune system mechanism where there is actually a protein in the host that purposefully puts mutations into the genome of the virus. A article mentions that APOBEC3 (APO-protein B mRNA editing enzyme catalytic sub-unit 3a or a3s) enzymes are innate immune effectors that introduce mutations into viral genomes. These enzymes are cytidine deaminases which transform cytosine into uracil. They preferentially mutate cytidine preceded by thymidine making the 5'TC motif their favored target [9].

It can be understood that these mutations may simply be the result of battle scars of this virus going through a reservoir of a population of either animals or humans that is perpetrating on its genome. It's unclear whether or not these mutations are conferring on the virus any extra abilities. Now it could be that these 500 cases, the reservoir could be humans or it could also be primates or rodents or even rabbits, we are not sure of the reservoir, we are not sure what the virus is infecting that is causing it to accumulate so many of these mutations. In the West African variant, where there is a relatively low mortality, there has not been any deaths reported so far in this outbreak. However, what is concerning is that at the same time that this was happening in West Africa and specifically Nigeria, in the Democratic Republic of Congo which has the more virulent version of the virus, there have been 1200 cases and in that cohort, there's been reported 58 deaths.

This type of monkey-pox variant that is endemic now in West Africa and specifically Nigeria since 2017 spreads with certain behaviour and that would imply that certain precautions need to be taken. Its unclear that whether

or not condoms would prevent this type of spread because unlike HIV which spreads through bodily fluids and semen specifically, monkey-pox spreads through the transmission of the open-source, even in contact with clothing or sheets that were in contact with people that were infected with monkey-pox.

At this point, it's unclear exactly what we can do to prevent other than avoiding people with monkey-pox if we can identify who they are but it shouldn't be lost that obviously a good immune system is going to be very helpful in preventing the worst types of monkey-pox clinical symptoms.

In a paper published in 2008 reminds that most viral issues with the human body become issues because the viruses are able to suppress our immune system. According to this abstract, Although monkey-pox virus-specific CD4+ and CD8+ T cells could recognize vaccinia virus (VV)-infected monocytes and produce inflammatory cytokines such as IFN $\gamma$  and TNF $\alpha$ , they were largely incapable of responding to autologous monkey-pox infected cells [10].

About the strain of the monkey-pox that is growing out now compared to the outbreak that was seen in the United Kingdom, Singapore and Israel in 2018 and 2019, it was seen that there is a draft sequence of the virus and its kind of a general draft sequence, so they can look at it to see if there's anything that has looked like what they're currently seeing right now. It was found that the draft sequence of the virus responsible for the rapidly growing monkey-pox outbreak shows that it is most closely related to strains detected in UK, Singapore and Israel in 2018 and 2019. It goes on and mentions that what isn't clear yet however is whether or not the virus has any changes that make it more transmissible in humans which could explain why the current outbreak is so widespread and by far the largest seen outside of the Central and West Africa where the virus spreads in monkeys. This could take some time to establish given

that monkey-pox has a large and complex genome [11].

From all this, we can understand that, even though we have learned about monkey-pox now because it's in industrialized nations, this outbreak actually started before SARS-CoV-2 and the current genome in the 2022 current outbreak based on the former outbreak in 2017 tells the story about what's been going on, where it's been and where it came from. Authorities say that the risk to the general public is low and they are urging any suspected cases to self-isolate immediately. WHO says that the general public should be aware of unusual skin rashes and experts suggest that there is no need of alarm.

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