

Why to be serious about monkeypox virus

Tapas Goswami^{1*}

¹Department of Microbiology, Institute of Veterinary Science & Animal Husbandry, Siksha 'O' Anusandhan (Deemed to be University), Bhubaneswar -751 030, India

Genetic research has opened a new path to rewrite the history of disease occurrence. After years of exhaustive screening of viral DNA from ancient humans, the international research team have suggested that as far back as AD 600, humans were infected with smallpox, and other viruses existed much earlier than suspected (Spinney, 2022). Monkeypox outbreaks typically occur in populations who hunt, kill, handle and consume bushmeat (Meyer *et al.*, 2002). Outbreaks start when someone comes in contact with an infected man or animal. Till May 2022, multiple cases of monkeypox have been identified in several non-endemic countries, such as Portugal, the United Kingdom, Spain, Sweden, Belgium and the United States of America. What does history tell us about the current outbreak of monkeypox? Somehow this outbreak is quite different and needs to be reevaluated with present epidemiological data. Virologists refer to it as the "little cousin" of smallpox in part because it causes an illness that is clinically indistinguishable from smallpox. Here is what we know so far.

Monkeypox a misnomer

Monkeypox is a zoonotic sylvatic zoonosis with incidental human infections. The question arises where does it come from? Is it a pox virus in monkeys? The answer is definitely No! To be honest, the name is a little bit of a misnomer; better, it should be called rodent pox. The natural reservoir of monkeypox remains unknown. Interestingly monkeys aren't major carriers; instead, the virus likely persists in squirrels, pouched rats, dormice or other rodents. However, non-human primates (like monkeys) may harbour the virus and infect people. The causative agent of monkeypox is

grouped under the orthopox virus genus; the same genus also includes variola virus (causes smallpox), vaccinia virus (used in the smallpox vaccine), and cowpox virus. The symptoms are very similar to those seen in the past in smallpox patients, although it is clinically less severe (Fig. 1., source Rimoin *et al.*, 2010).

Past is not last

The past history of pox viruses offers some clues as to what can be predicted from smallpox's kin in the future. Historically 60 per cent of the pathogens that plague humankind, including the orthopox viruses, have originated from other vertebrates. Monkeypox is not a new disease. In 1958, two outbreaks occurred in colonies of monkeys kept for research, which were the first documented cases of the illness, and the name "monkeypox" came from it (www.cdc.gov). The first human case of monkeypox detected in a child suspected of having smallpox was recorded in 1970 in the Democratic Republic of the Congo (DRC), the period when intensified effort to eliminate smallpox was in progress. In 1968 the Taterapox virus (TATV), a phylogenetically closely related virus to variola, the etiologic agent of smallpox, was isolated from an apparently healthy wild gerbil (*Tatera kempi* or *Gerbilliscus kempi*) in Africa (Lourie *et al.*, 1975). Despite the similarity, *in vivo* studies have shown that TATV can infect several animals but produces an inapparent infection in wild-type mice; however, TATV causes morbidity and mortality in some immunocompromised strains (Parker *et al.*, 2017). In early 1970, the most difficult task was to prove that monkeypox is a different virus from smallpox. With persevering effort, Professor Frank Fenner proved that monkeypox is another

*Corresponding Author, E Mail: goswami.tapas@gmail.com

pox group of viruses and is not so virulent as human pox (Goswami, 2011). On 8th May 1980, the WHO assembly announced that smallpox had been eradicated. With the subsequent cessation of smallpox vaccination recently, monkeypox has emerged as a threat to public health.

Circulating virus silent or violent

Very recently, a monkeypox outbreak, the first case reported on 7th May, 2022 in UK, is a subject of concern among public health officials. As of now when the present manuscript is about to publish and ready for printing the number of confirmed cases of monkeypox has gone up to 920 and suspected cases are 70 in number (Kraemer *et al.*, 2022). Out of all these large numbers of confirmed cases, the majority of cases are from Portugal, Spain and United Kingdom. The occurrence of monkeypox in Africa, typically in the western and central parts of the continent, is not uncommon. However, the appearance of this virus in separate populations across the world where it doesn't usually surface is alarming, and researchers are in the race for the answer. The identification of confirmed and suspected cases of monkeypox with no direct travel links to an endemic area represents a highly unusual event. Monkeypox endemic countries are Benin, Cameroon, the Central African Republic, the Democratic Republic of the Congo, Gabon, Ghana (identified in animals only), Ivory Coast, Liberia, Nigeria, the Republic of the Congo, Sierra Leone and South Sudan (WHO, 2022). Monkeypox is a nasty illness; it causes fever, body aches, enlarged lymph nodes and eventually "pox," or painful, fluid-filled blisters on the face, hands and feet. Most people recover from monkeypox in a few weeks without treatment. One version of monkeypox is quite deadly and kills up to 10% of people infected. The high transmissibility of this virus is evident, but it does not necessarily make it lethal. Almost 30 years after the eradication of smallpox, the incidence of human monkeypox has increased in the DRC (Rimoin *et al.*, 2010, Fig.1.). Monkeypox is mostly a mild, self-limiting disease lasting two-to-three weeks. However, in some cases, it can cause



Fig. 1. Human Monkeypox

death. Still, it is puzzling why pox viruses vary so greatly in their severity. The fatality rate "in recent times" has been found to be around 3 to 6% as per WHO report. Most of the people contracting cowpox, camelpox and raccoon pox are not severely affected. All these viruses trigger skin rash, with virus-filled pustules clearing up on their own without much harm. Monkeypox infections, on the other hand, can be quite deadly in humans. Not all monkeypox viruses are equally dangerous. There are two distinct genetic clades of monkeypox, the Central African (or Congo Basin) clade and the West African clade, which is milder than the central African one.

Repercussion of mutation

Monkeypox virus is a relatively large-sized DNA virus. In comparison to RNA viruses DNA viruses have better ability to check any genetic mistake in its genome during viral replication and smart enough for repairing the mistake in the newly synthesized DNA of progeny virus; so its mutation rate is bit slower. Therefore, it's unlikely that the monkeypox virus has suddenly mutated to become adept at human transmission. Neither monkeypox virus jumped from monkey to human nor monkeys are major carriers of the disease. After a detailed study of the monkeypox outbreak in the DRC, in 1977, the WHO reported that the virus appeared to be changing its pattern of infection with much

higher rates of person-to-person transmission (WHO, 2022). The recent outbreak has indicated that the severity of the disease is governed by two major traits of the virus; one is the virulence of the strain, and the other is its transmissibility. We don't know what exactly it is. According to one school of thought, there is ample opportunity for simultaneous infection of a human or other vertebrate host with a poxvirus and a retrovirus which may modify the pox viral genome. Retroviruses are very well known for incorporating their own genes into their host's DNA. About 8 per cent of the human DNA consists of DNA of retroviral origin. On the other hand, poxviruses are genetically stable and do not mutate quickly. If they can snip genes from their hosts that make them more virulent, then dangerous threats could occur more frequently in an unpredictable manner beyond expectation.

Deadly or friendly, why so

Why is smallpox more deadly than monkeypox? Look at genes; there is sin. Delicate genetic differences between the two genetic clades of monkeypox explain the shifting severity of pox infections. To be precise, some poxviruses carry specific genetic elements coding for specific proteins that coordinate the immune system to respond effectively to the infection. When researchers compared the genes from different poxviruses, they could able to narrow it down to one particular gene in several different kinds of poxviruses. In the deadliest strains of variola, this gene triggers the production of a protein that possibly prevents some immune cells from counter attacking against the virus (Likos *et al.*, 2005). But the equivalent gene in the Congo Basin strains of monkeypox (which are less deadly than smallpox) code for a truncated (much shorter form) protein. While scanning the milder West African version of monkeypox, the exact gene is missing altogether; consequently, the protein in question is not synthesized at all. All of these indicate that the shorter protein in the Congo Basin strains of monkeypox somehow made them less deadly than smallpox. The gene

responsible for coding a shorter peptide or complete lack of that particular gene is the critical decision-maker for lethality. The West African monkeypox virus is considered to be milder than the central African one.

Reservoir

Analysis of genome sequencing data suggests that the evolutionary ancestor of smallpox probably originated in an African rodent species, possibly now extinct. Similarly, cowpox and monkeypox, despite their names, persist and remain living in voles, squirrels or other wild rodents. Unlike smallpox, cowpox and monkeypox naturally skulk in rodents and other creatures, so they can never be entirely eliminated. When variola's ancestor first jumped into humans, it probably was not very contagious, says microbiologist Mark Buller of Saint Louis University. Then it is assumed that a more transmissible variant form has emerged. The critical change allowed the virus to broadcast itself via the coughs, exhalations or sneezes of an infected person. Biological alteration and climate change gave the emerging virus the edge it needed to become a global scourge (Shah, 2013). The monkeypox virus has only been isolated twice from an animal in nature. Monkeypox can be produced experimentally in the cotton rat, but these animals succumb quickly to an injection of the virus and are useful for testing antiviral drugs and for studying the virus's lethal effects. Another animal model for monkeypox is Prairie-dog that belongs to *Sciuridae* (squirrel) family and offers hope of tackling the monkeypox virus (Knight, 2003).

Why to be concerned

People with no apparent connection to one another still, monkeypox detected in those people advocate that the virus might have been spreading silently. A person infected with monkeypox hardly goes unnoticed because of the prominent skin lesions it causes. If there is a chance of spreading asymptotically, it may cause disaster because it would make the virus harder to track. Monkeypox is not a

sexually transmitted disease, but sexual activity establishes close contact. Therefore, the chance of infection to the partner is more. But most puzzling is that almost all the cases reported from a cluster of men in 20-50 age group who are gay, bisexual and have sex with men (GBMSM) is perplexing for the scientific community (Kozlov, 2022). The first reported case recently travelled to Nigeria, an area affected by monkeypox, but many of the recently infected people had no history of travel, indicating human-to-human transmission within the community. In everyone's mind, the biggest question is how the virus is transmitted from person to person, but no definite answer is there.

Diagnosis

For an accurate diagnosis, a differential diagnosis must be made to exclude chickenpox and measles. For accuracy, the preferred laboratory test is polymerase chain reaction (PCR). PCR should be conducted from the samples collected from the roof or fluid from vesicles and pustules and dry crusts of skin lesions. Serologically cross-reactive, antigen and antibody detection methods do not provide monkeypox-specific confirmation. Remote vaccination with a vaccinia-based vaccine might lead to false-positive results (WHO, 2022). First draft genome sequence of monkeypox virus (52.1 kb genome size) derived from confirmed cases of recent outbreaks reported from Portugal during May, 2022, affecting multi countries belonging to the West African clade. The sequence is most closely related to viruses associated with the exportation of monkeypox virus from Nigeria to several countries in 2018 and 2019, namely the United Kingdom, Israel and Singapore. The detail of the genome sequence data was uploaded to the public domain by researchers from Portugal on 19th May, 2022 (Isidro *et al.*, 2022).

Treatment

Currently, no approved drug for monkeypox is licensed. As on date, two orally

bioavailable drugs, brincidofovir and tecovirimat, have been approved in the USA for the treatment of smallpox in the event of bioterrorism (FDA 2021). Human efficacy trials are uncertain; however, both drugs demonstrated efficacy against other orthopoxviruses (including monkeypox) in animal models (Grosenbach *et al.*, 2018). An extended programme to assess the efficacy of tecovirimat is in progress in the Central African Republic, where monkeypox outbreaks are common, as cited in the literature (Alder *et al.*, 2022).

Vaccination

The smallpox vaccine can provide 85% protection against monkeypox. A new modified attenuated vaccinia virus (Ankara strain) was approved for the prevention of monkeypox in 2019. This is a double-dose vaccine for which availability remains limited. Smallpox and monkeypox vaccines are developed in formulations based on the vaccinia virus due to cross-protection afforded for the immune response to orthopox viruses. One of the two available vaccines, manufactured by Emergent BioSolutions, USA, is designed as a smallpox vaccine and can protect even after exposure to the monkeypox virus. The Denmark-based vaccine company Bavarian Nordic contains a non-replicating form of vaccinia designed to cause fewer side effects. It requires two doses to be given weeks apart. Animal studies suggest that the first dose works faster than Emergent BioSolutions' vaccine; the second dose increases the durability of protection. It causes fewer side effects and is the only vaccine overtly approved for monkeypox (Cohen, 2022).

CONCLUSION:

Indeed, monkeypox is so rare that few doctors have ever seen a case. In the present situation, monkeypox is an emerging global health threat due to cross-border spread and onward rapid transmission due to flight mode human movement. Paediatric monkeypox infection is associated with severe disease and high mortality than in adults. One vaccine,

JYNNEOS™ (also known as Imvamune or Imvanex), has been licensed in the United States to prevent monkeypox and smallpox. It is unknown whether or not a person with severe monkeypox infection will benefit from treatment with either available antivirals, *viz.* Cidofovir and Brincidofovir. The effectiveness of vaccinia immunoglobulin (VIG) in the

treatment of monkeypox complications is cloudy (CDC, 2021). VIG can be considered for prophylactic use in an exposed person with severe immunodeficiency in T-cell function. According to the CDC, no specific treatments are available to cure monkeypox infection; whatever treatment is given, it is primarily for relieving symptoms.

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