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Review Article

SUMMARY OF MONKEYPOX INFECTION AND SOME FACTS FOR VETERINARIANS

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SUMMARY: Monkeypox is an emerging and neglected zoonotic disease. The importance of the disease has been highlighted in the recent past as there have been a significant number of cases reported in North America, South America, and Europe. The disease is caused by the monkeypox virus which belongs to the family of Poxviridae. The virus was identified in 1958 in captive monkeys at a research institute in Denmark and human infection was first identified in the Democratic Republic of Congo (DRC) in 1970. The first set of clinical cases of monkeypox outside the African continent was reported in the USA, UK, Israel, and Singapore. Two distinct clades of monkeypox virus have been identified and two models of transmission have been reported as animal to human and human to human transmission. The transmission occurs through direct contact, contaminated body fluids, and contaminated respiratory droplets. Generally, human gets the infection through direct contact with the infected animal or contaminated materials. Furthermore, human to human transmission of monkeypox has been reported through placental membranes, direct contact with skin, and through fomite. Nosocomial infection has also been reported in humans while speculatory evidence was found on sexual transmission in humans. The exact animal reservoirs of monkeypox have not been identified, non-human primates and rodents had been suggested for harbouring the virus in the environment as rope squirrels, tree squirrels, Gambian pouched rats and dormice. During the first five days, fever, lymphadenopathy, back pain, extreme headache, myalgia (muscle ache), and severe asthenia (energy shortage) are reported in the infected humans. The macular-papular lesions appear in the first 1 - 3 days of fever and develop into to fluid-filled blisters. The blisters rupture and crusts develop within 10 days. The non-symptomatic disease has been reported with an unknown prevalence in humans. Smallpox vaccines were shown to have cross protection against monkeypox infection in humans. In addition, the same vaccine can be used prophylactically since the vaccine reduces the emergence of clinical signs of monkeypox infection in humans. Furthermore, immunoglobulin derived from the vaccinia virus is also used as post-exposure therapy in an exposed population.

KEYWORDS: Monkeypox, Sri Lanka, Zoonotic, popular lesions, emerging zoonotic disease

INTRODUCTION

Monkeypox is an emerging viral disease in humans and the clinical picture is almost similar to the clinical signs of smallpox in humans (Berthet *et al*., 2021; Diaz, 2021; Heymann and Simpson, 2021). Importantly, monkeypox has become the most important pox viral infection in humans after the global eradication of smallpox (Sklenovská and Van Ranst, 2018). Although monkeypox is considered a neglected zoonotic infection in humans, the gravity of the disease has increased and emerged as a threatening disease in the world (Nakoune and Olliaro, 2022). Currently, monkeypox is considered one of the hot topics in the global health arena, consequent to the involvement of the universal media (Makhani *et al*., 2019). The disease is caused by the monkeypox virus which belongs to the family of Poxviridae (Berthet *et al*., 2021). The purpose of this review is to highlight the basic technical information on monkeypox among veterinarians in Sri Lanka.

Monkeypox was identified in 1958 while the human infection was first reported in the DRC in 1970 (Angelo *et al*., 2019; Petersen *et al*., 2019). The disease had been reported in a number of African countries in 2000 including Cameroon, Central African Republic, DRC, Liberia, Nigeria, Sierra

Leone and South Sudan (Angelo *et al*., 2019). The pox viral infection in humans such as smallpox has not been reported in humans since the last natural case in Somalia and laboratory-acquired case in England in 1977 and 1978 respectively (Russo *et al*., 2021). Consequently, there was no significant discussion on pox viral infection in humans for a number of decades until the emergence of monkeypox just after the COVID-19 pandemic in the world. In monkeypox, the first clinical case**s** outside of Africa were reported in the USA (2003 and 2021), the UK (2018, 2019), Israel (2018) and Singapore (2019) (Hobson *et al*., 2021). Monkeypox was reported in isolation at the premises of COVID-19 in UK, and significant attention was directed to further prevention of the disease in the community (Hobson *et al*., 2021). Chickenpox, caused by the varicella-zoster virus which belongs to the family Herpesviridae was also misdiagnosed as monkeypox due to the similar clinical picture. A similar incident was reported in Singapore, Monkeypox was differentiated from Chickenpox only after DNA sequencing (Tumewu *et al*., 2020).

Epidemiology

Monkeypox is a double-stranded, brick shaped, DNA virus, and it multiplies in the cytoplasm of the infected cell (Alakunle *et al*., 2020). The monkeypox virus is included in the Genus Orthopoxvirus under the family of Orhopoxviridae. There are 12 species in the Genus including the Variola virus which causes smallpox in humans. Mammals and arthropods are the natural hosts of Orthopoxvirus which included smallpox, cowpox, horsepox, camelpox and monkeypox. Two distinct clades have been identified globally in monkeypox as virulent Congo basin clade and the milder West African clade (Adalja and Inglesby, 2022). It is early to have comprehensive summary on epidemiology of monkeypox since extensive studies have not been carried out in humans. However, current understanding is based on outbreak reports, case reports and passive intermittent surveillance studies in the literature (Ihekweazu *et al*., 2020). Basically, two methods of transmission had been observed in monkeypox as animal to human and human to human (Alakunle *et al*., 2020). The transmission occurs in humans through direct contact, contaminated body fluids and through contaminated respiratory droplets (Berthet *et al*., 2021). In addition, cutaneous, musculocutaneous and placental routes of transmission were reported in humans (Beer and Rao, 2019). Furthermore, nosocomial infection of the monkeypox virus has also been reported and strong evidence was found on sexual transmission in humans (Reynolds *et al*., 2019; Alakunle *et al*., 2020; Nakoune and Olliaro, 2022). Importantly, the disease had been transmitted to hospital workers from a patient in the UK (Vaughan *et al*., 2020).

Initially, monkeypox was diagnosed among bush meat makers and consumers in Africa and the disease moved to Europe with international migration (Beer and Rao, 2019). Monkeypox outbreaks occurred among humans closely associate with live animals in rainforests of West Africa, the disease was self-limiting and a chain of human transmission ends without forming an epidemic (Heymann and Simpson, 2021). Some clinical cases were related to the handling of live animals or hunting in endemic regions (Heymann and Simpson, 2021). In addition, epidemic risk in humans is considered low in monkeypox infection (Heymann and Simpson, 2021). Furthermore, the transmission efficiency of the monkeypox virus was 10 times lower than smallpox in humans (Reynolds *et al*., 2019). In mathematical modelling done in DRC, the virus was shown a low epidemic potential since the R_0 was 1.10 to 2.13 (Heymann and Simpson, 2021). Monkeypox was found common in children than in adults in Africa (Beer and Rao, 2019). Furthermore, monkeypox is named as an underreported or misdiagnosed disease among the susceptible and endemic populations in the world, mainly due to the lack of awareness (Silva *et al*., 2020). Importantly, the disease was common among children who were not vaccinated against the smallpox virus in Africa previously (Adalja and Inglesby, 2022). The outbreaks were found common in rural areas (less than 1000 people in a village) where near the tropical ever-green forest in Africa (Beer and Rao, 2019). The mortality rate of monkeypox was low; the highest mortality rate reported in Africa was 10%. (Nakoune and Olliaro, 2022). As described previously, two major strains were reported in monkeypox as West African strain and the Congo basin strain (Sklenovská and Van Ranst, 2018). The Congo basin strain was shown to cause 10-30% mortality while the West African strain was reported to cause low mortality of 1% (Sklenovská and Van Ranst, 2018). The annual average attack rate of monkeypox had been estimated as 1.7 per 10,000 in

unvaccinated humans while it was as low as 0.04 per 10,000 in a vaccinated population (Petersen *et al*., 2019). The incidence rate of monkeypox in humans has increased from 0.64 to 2.82 (per 10 000) in 2001 and 2013 respectively (Bunge *et al*., 2022). In 2016, the incidence rate was 50 for 100,000 humans in DRC (Bunge *et al*., 2022). However, the latest outbreaks were limited in Europe and North America, although few cases were reported in the rest of the world (Mahase, 2022). In fact, the incidence rate needs to be recalculated considering all countries and it should not be limited to certain areas of the globe.

The current monkeypox outbreak has spread to common tourist destinations and travel-related cases were reported from many countries in Europe and North America (Adalja and Inglesby, 2022). According to the Centre for Infectious Disease Research and Policy (CIDRAP) (30th April 2022), 226 cases had been reported from 26 different countries in the world; it is envisaged that monkeypox will be reported in the rest of the countries near future. The most of new cases have been linked to the migration of people and travelling routes from the endemic regions while a few cases of unlinked and undetected transmission have also been reported (Adalja and Inglesby, 2022). The disease was frequently reported in sexually active populations and most of the cases were reported in homosexual men (Petersen *et al*., 2019). Both sexual or/and transmission through skin contact were reported during the current outbreak (Adalja and Inglesby, 2022). No sufficient research has been conducted to determine whether a new viral strain is responsible for the current outbreak as a result of mutation from the original monkeypox virus (Adalja and Inglesby, 2022).

A definitive animal reservoir for the monkeypox virus has not been identified and non-human primates, rodents, rats, and squirrels were suggested to harbour the virus (Besombes *et al*., 2019; Berthet *et al*., 2021). In chimpanzees, the clinical disease has been mostly reported as a severe respiratory infection although the cutaneous vesicle development was low (Patrono *et al*., 2020). The monkeypox virus had been isolated in the faeces of chimpanzees and flies; hence, faecal contamination of chimpanzees and other primates may have a role in spreading the disease in the environment (Patrono *et al*., 2020). Therefore, as association with wildlife may play a vital role in spreading the disease to closely associated people, identification of the role of individual species in harbouring the virus needs to be further investigated. According to the Centres for Disease Control and Prevention, the virus had been isolated in reservoirs only on limited occasions. The reservoirs have been identified through outbreak investigations, ecologic analysis, anthropologic information and laboratory studies of reservoir competence, and further investigations are required for a better conclusion (Reynolds *et al*., 2019). The disease has been reported in Thomas's rope squirrel, sooty mangabey and chimpanzees in Africa (Besombes *et al*., 2019; Berthet *et al*., 2021). Interestingly, cynomolgus monkeys, adult white rabbits, and white rats were shown to be refractory to monkeypox viral infection (Parker and Buller, 2013; Reynolds *et al*., 2019). Some of the animal species that are used as pocket pets, laboratory animals and some field animals including Gray short-tailed opossum, Southern opossum, African hedgehog, while rabbits, New World giant anteater, chinchilla, cotton rats, jerboa, African dormouse, house mouse, laboratory mouse, multimammate mouse, Rufus-nosed rat, dormice, giant-pouched rat, Black-tailed prairie dog, rope squirrel, sun squirrel, groundhog, 13-Lined ground squirrel, Red squirrel, unstriped ground squirrels, marmoset, guenons, colobuses, sooty mangabey, gorilla, chimpanzee, orangutan, four-toed sengis, Sende, African civet and elephant shrews were suggested as natural reservoirs of monkeypox virus (Besombes *et al*., 2019; Reynolds *et al*., 2019). Primary infection of monkeypox is mostly associated with close contact with the wild fauna, while secondary transmission occurs due to close contact within the community (Besombes *et al*., 2019). Monkeypox virus multiplies in reservoirs and sheds for an extended period via various routes. Some of these animals are consumed by humans as an alternative protein source; a possible opportunity of contact with humans (Reynolds *et al*., 2019). A fairly large outbreak was reported (with 47 confirmed cases) as a result of the importation of rodents from Ghana to the USA and those rodents were reared as pets in households (Ye *et al*., 2019). Furthermore, the importation of rodents resulted in spreading the virus to domestic or endemic rodent pets in North America such as North American prairie dogs (*Cynomys spp.*) (Petersen *et al*., 2019). Reinforcing surveillance has also been recommended in Central

Africa due to the rising number of outbreaks and fatality percentage (Kalthan *et al*., 2018).

Over 400 chimpanzees are being slaughtered every year in Central Africa for human consumption (Devaux *et al*., 2019). In addition, Orangutan is a popular dish in Indonesia. Furthermore, the consumption of meat of non-human primates was found among the group of people in the low poverty line in Africa, Asia and South America (Devaux *et al*., 2019). Smuggling of bush meat in several international airports has been reported due to the high demand in Western countries (Devaux *et al*., 2019). The specimens of chimpanzees (Pan troglodytes), mangabeys (Cercocebus), guenons (Cercopithecus), baboons (Papio) and green monkeys (Chlorocebus) had been found in many international airports (Devaux *et al*., 2019). Heavy deforestation resulted in the fragmentation of 60% of tropical rainforest into 45% of land in Central Africa. In fact, habitats of non-human primates have been reduced in three countries in Central Africa namely, Guinea-Bissau, southern Senegal and western Guinea (Bersacola *et al*., 2018). Consequently, disease transmission from non-human primates to humans has increased in this interface of human to non-human primates (Afelt *et al*., 2018; Devaux *et al*., 2019).

It has been noted that the majority of patients who were infected with the monkeypox virus were less than 30 years of age in Nigeria, mostly due to the lack of cross-protection with low levels of antibodies resulting from the discontinuation of smallpox vaccination (Petersen *et al.*, 2019). The incubation period of the monkeypox virus is 5-21 days in humans (usually 6-13 days in most of the clinical cases); the infection appears as a skin rash and desquamation appears 4 weeks later (Heymann and Simpson, 2021). Although the exact reason for the seasonal variation of the infection has not been identified, dependent factors such as rainfall and other ecological elements may have an effect on the behaviour of reservoir animals, movement of bush meat species and the routine of hunters in Africa (Mauldin *et al*., 2022).

Clinical signs

The clinical signs of monkeypox consist of lymphadenopathy, macular papular rash in the palms of the hand and soles of the feet of humans (Berthet *et al*., 2021). In the first 5 days of the infection, fever, lymphadenopathy, back pain, extreme headache, myalgia and serious asthenia were reported in patients (Petersen *et al.*, 2019). Macular papular lesions appear in the first 1 to 3 days of fever leading to the formation of fluid filled blisters and those blisters burst and crusts develop over them within 10 days (Petersen *et al.*, 2019). Occasionally, the blisters may end up as pus-filled vesicles (Petersen *et al*., 2019). Severe clinical complications such as genital ulcers, body aches, headache, sore throat, pruritus, conjunctivitis, photophobia, nasal congestion, cough, skin ulcers, haemorrhagic skin lesions, scrotal oedema, hepatomegaly, nausea and vomiting are observed in a limited number of infected patients (Ogoina *et al*., 2020). In addition, gastroenteritis, sepsis, bronchopneumonia, encephalitis, keratitis and intrauterine foetal death have been reported (Ogoina *et al*., 2020). Lymphadenopathy was shown to be common in different sites including cervical, sub-mandibular, inguinal, axillary; a generalized infection in multiple lymph nodes has also been found (Ogoina *et al*., 2020). In addition, anxiety and depression were found in infected humans (Ogoina *et al*., 2020). Importantly, the virus had been isolated in lesions on the tongue, skin, lungs, and eyelids (Hutson *et al*., 2007). In addition to miscarriage and embryonic death reported in pregnant women, some have given birth to normal infants too (Mbala *et al*., 2017). The stillbirth or macerated foetuses were found with cutaneous macula-papillary skin lesions in the head, trunk and extremities (Mbala *et al*., 2017). In contrast, the non-symptomatic disease has been reported with unknown prevalence (Guagliardo *et al*., 2020; Simpson *et al*., 2020).

The clinical outcome and mortality rate of monkeypox in humans may associate with available medical facilities in the region. The blisters emerged in the mouth, spread to the face and ultimately to the soles and palms of the patient (Adalja and Inglesby, 2022). Conversely, the severity of infection was shown to be high in HIV infected patients, including prolonged infections, larger vesicles and multiple secondary infections (Ogoina et al., 2020). Although possible treatment protocols were not discussed in this paper, successful treatment strategies are applied in infected humans worldwide. The antiviral treatment was shown to be a success with “tecovirimat” in USA and with “brincidofovir” in UK (Adler *et al*., 2022 Rao *et al*., 2022).

Prevention and control of monkeypox

Smallpox vaccines were cross protective against monkeypox infection in humans; prophylactic usages of the smallpox vaccines minimise the emergence of clinical signs of monkeypox infection in humans (Adalja and Inglesby, 2022). Furthermore, immunoglobulin derived from the vaccinia virus had been used as post exposure therapy (Adalja and Inglesby, 2022). Reynolds *et al.* (2019) have formulated guidelines and instructions to minimize the risk of monkeypox virus in humans in detail, and one health approach has been highlighted and encouraged to reduce the risk of human infection in the endemic region (Reynolds *et al.* 2019). Lack of systematic and longitudinal surveys, underdeveloped disease surveillance, lack of laboratory capacity, the lag between detection of infection and laboratory confirmation, lack of animal disease data, lack of predictive disease risk modelling at community level, lack of understanding of the natural history of the monkeypox virus and lack of comprehensive strategy of vaccine utilization have been identified as potential weaknesses in monkeypox prevention and control in African environment (Reynolds *et al*., 2019). In addition, risk analysis of monkeypox viral infection, population genetic studies, longitudinal studies in suspected reservoirs with the environments, ecologic risk mapping, modelling of monkeypox viral transmission, and survey and surveillance on high-risk communities have been suggested by the experts to minimise the risk of monkeypox virus in human (Reynolds *et al*., 2019). In a situation in which monkeypox is detected, continued monitoring of healthcare workers is strongly encouraged. However, monitoring and post exposure prophylaxis of monkeypox in healthcare settings ended up with a success story in Singapore previously (Kyaw *et al*., 2020). However, the risk of disease transmission to healthcare workers from the infected patients was shown to be low (Kyaw *et al*., 2020).

A new vaccine for monkeypox is in the pipeline although a long time is required for experimental and clinical trials (Petersen *et al*., 2019). Ankara strain of modified live attenuated vaccinia virus is also recommended to prevent the disease since 2019 (WHO, 2022). However, pre-preparation is always encouraged to prevent entering new infectious agent into a country or a geographic location or community. Sharing experiences with other territories where the same organism became an issue would be a better start for any country to prevent and control an infectious agent in the world. Pre-preparedness in the local community has been identified as an effective awareness tool in disease epidemiology. As an example, outbreak management of monkeypox with community participation had been tried in Nigeria with significant success. In addition, genetic-based epidemiological studies on spreading monkeypox from Nigeria to the UK had also been studied (Silenou *et al*., 2020; Mauldin *et al*., 2022). Nevertheless, antiviral therapy and vaccination with new generation non-replicating smallpox vaccines have been identified as an efficient tool to control the disease in the susceptible or vulnerable human population (Simpson *et al*., 2020). Lack of awareness is a vital obstacle against emerging infectious agents such as monkeypox, and only 10% to 36.5% of general practitioners in Indonesia had a sound knowledge of monkeypox (Harapan *et al.*, 2020). Further, the cross-sectorial approach has been highly recommended by experts; may be a sound solution against the current fear of monkeypox moving across the globe (Eltvedt *et al*., 2020).

The situation in Sri Lanka with regard to monkeypox

Monkeypox was reported in Sri Lanka in late 2022 (4th November 2022) and only a few cases have been reported. The health sector laboratories are equipped with standard diagnostic tools for the diagnosis of monkeypox in Sri Lanka. Some veterinary diagnostic laboratories have established diagnostic facilities against the diseases. Raising awareness among possible risk populations, strengthening the diagnostic facilities and improvement of quarantine facilities to screen humans and animals have been identified as major components of the prevention and control of monkeypox in Sri Lanka. Tourism is the main mode of transmission of monkeypox to the country which warrants more attention. Awareness of monkeypox needs to be increased among high-risk groups in the country such as sex workers, workers who have close contact with tourists such as tour guides, hotel workers, health workers, sanitary workers etc. In addition, fishermen are also considered as the risk group due to the social interaction between Sri Lankan and Indian fishermen. Importantly, monkeypox has been reported with mortality in Kerala, India recently. Proactive plans for monkeypox prevention may be

required although it has not been identified as a major disease in Sri Lanka yet. In addition, improvement of diagnostic laboratory facilities and awareness on the disease under the one health concept both in human and veterinary sector services are an absolute necessity. Although no published evidence is found, non-human primates seem to be slaughtered illegally in certain communities. It is believed that beef is replaced by bush meat originating from non-human primates at rural food outlets on main travel routes in the country. Thus, raising awareness among hunters, dealers and other individuals regarding the dangers of contracting monkeypox due to these practices should need much attention of the relevant authorities to prevent this disease from spreading in the country.

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