Review Article

Reminiscing the recent incidence of monkeypox in Nigeria: Its ecologic-epidemiology and literature review

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Abstract

Monkeypox (MKPX) is a rare viral zoonosis which was first discovered in a laboratory in Denmark in 1958. This critical review involved literature search of data on the history of MKPX virus (MKPXV), its emergence and re-emergence, molecular virology, global epidemiology and geographical distribution, the recent outbreak of MKPX in Nigeria, diagnostic and treatment considerations using Google Scholar, PubMed and Scopus. Findings from this review revealed that the first human cases of MKPX were diagnosed and differentiated from smallpox in the early 1970s. Since this period, several cases have been reported in rural, rainforest areas of West Africa and the Congo Basin, especially in the Democratic Republic of Congo, Cote d'Ivoire, Cameroon, Midwest of the United States of America, South-Sudan, Central African Republic, and recently in Nigeria. The outbreaks in the non-endemic areas of the US and Sudan occurred due to zoonotic transmission of the virus into these nonrain forested areas. The geographical spread of MKPXV until date has renewed research efforts in unravelling environmental factors that favour ecological niche of this pathogen. This study aimed to review both biotic and abiotic factors that are responsible for the expansion of the ecological niche and geographic distribution of human MKPX in Nigeria. It appears that environmental factors, conflict and globalisation are responsible for the increasing risk of animal-human transmission through direct contact between the cutaneous or mucosal lesions of the infected animal and the compromised skin barrier of a human, and the consumption of poorly cooked-infected flesh. Lymphadenopathy is a distinguishing clinical feature of MKPX from other pox-like illnesses. Laboratory diagnosis of anti-poxvirus antibodies in an unvaccinated person with a clinical history of severe illness and total body rash is suggestive of MKPX infection. The lack of sufficient data to guide the identification of potential reservoir hosts, and public health intervention strategies/surveillance, inadequate training for health workers, unavailability and inaccessibility of suitable diagnostic assays, vaccines and anti-viral treatment could be some of the reasons cases of MKPX re-emerge when not successfully contained, especially in endemic regions.

Keywords: Monkeypox virus, Nigeria, re-emergence, zoonosis

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INTRODUCTION

Monkeypox virus (MKPXV) is a double-stranded DNA virus and one of the human pathogenic orthopoxviruses that include *Variola* (VARV), cowpox (CPX) and *Vaccinia* (VACV) viruses. Less well-known members include ectromelia, camelpox and cowpox viruses.[1] Human Monkeypox MKPX is clinically almost identical to ordinary smallpox, and therefore, since the global eradication of smallpox in 1980, much attention has been paid to MKPX as a smallpox-like disease and possible agent of bioterrorism. Additional attention was brought to bear on this virus when, in the spring of 2003, it emerged for the first time in the Western Hemisphere and caused a cluster of cases in the US Midwest.[2] The virus causes a disease that manifests similarly to smallpox, but with milder morbidity and lower mortality rates.[1,2] Variation in MKPXV virulence, genetics and pathological differentiation has been observed and mapped to defined geographic origins of virus isolates from Central Africa (Congo Basin) and those isolates from Western Africa.[1,2]

MKPX is similar in presentation to smallpox with the addition of notable lymphadenopathy in the majority of patients. Symptoms of MKPX closely resemble those of smallpox and include a febrile prodrome followed by the development of a disseminated vesiculopustular rash with blisters and crusts over the body.[3] MKPX patients are vulnerable to secondary bacterial infection, dehydration, encephalitis, bronchopneumonia and blindness due to corneal scarring from lesions.[4,5]

A direct contact or exposure with ill, prairie dogs (a group of herbivorous burrowing rodents), showing signs of profuse nasal and ocular discharge, dyspnoea, lymphadenopathy and mucocutaneous lesions was noted among the cases reported during the 2003 outbreak in the US.[6] This was the first time human MKPX was reported outside of Africa. Investigators determined that a shipment of animals from Ghana, imported to Texas on April 9, 2003, introduced MKPXV into the United States. The shipment contained approximately 800 small mammals representing nine different species, including six genera of African rodents. Centres for Disease Control and Prevention (CDC) laboratory testing using polymerase chain reaction (PCR) and virus isolation revealed that two African giant pouched rats, nine dormice and three rope squirrels were infected with MKPXV. After importation into the United States, some of the infected animals were housed in close proximity to prairie dogs at the facilities of an Illinois animal vendor. These prairie dogs were sold as pets before their developing signs of infection.[6]

Another interesting observation noted among those cases was the presence of a common animal distributor where prairie dogs were housed or transported along with African rodents from Ghana.[7] Reports have later confirmed that most cases of MKPX were associated with exposure to these rodents, the local Gambian rats, which were the native habitat of Africa although these rodents are not reservoirs of MKPXV.[7] After an exposure, and an average incubation period of 12 days, the animal became ill and has a potential to transmit the virus to humans, when present in close proximity. Human-to-human, disease transmission leading to an outbreak was reported from the Democratic Republic of Congo (DRC) during 1996–1997. Studies reported from this outbreak suggested that within households, MKPXV was secondarily transmitted to 8%–15% of human contacts.[7] MKPX was identified as an important worldwide health problem, human infection rates were under-reported, and this undermined their significant role in the pathogenesis. Analysis of the 2003 US outbreak implicates animal-to-animal and animal-to-human transmission as the significant modes of transmission. However, experiences in a recent human MKPX outbreak showed that human-to-human transmission of this virus is apparently possible especially in Central Africa, where the burden of household transmission cannot be overlooked. No occurrence of human-to-human transmission has been reported in West Africa. Some recent findings have revealed the presence of mechanisms of immune evasion that allow the virus to spread systemically and sometimes to remain dormant for long periods.[6,7] These mechanisms, which may be present in variola as well, cause the induction of a state of unresponsiveness in CD4+ and CD8+ T cells when they interact with MKPXV –infected cells. The process seems to be MHC-independent.[2,6,7]

The route of infection can be percutaneous, through bites or scratches of infected animals or during manipulation of infected material, or through respiratory or mucosal routes. In African endemic regions, the spread of the infection is related to the hunting, skinning, preparing and eating of infected rodents and monkeys.[3,7]

CLASSIFICATION AND CHARACTERISATION OF MONKEYPOX VIRUS

The MKPXV belongs to *Poxviridae* family, which also includes cowpox, vaccinia and variola (smallpox) viruses. Poxviruses are the largest vertebrate viruses known, infecting humans, and other vertebrates (species of sub-family *Chondropoxvirinae*), and arthropods (species of sub-family *Entemopoxvirinae*). There are around 70 known species of poxviruses spread among 28 genera and two subfamilies

(the *Chordopoxvirinae* and the *Entomopoxvirinae*). The virions contain a linear double-stranded deoxyribonucleic acid genome and enzymes that synthesize messenger ribonucleic acid. They multiply in the cytoplasm of the host cells.[7]

The *Chordopoxvirinae* consists of around ten genera including the genera which are genetically and antigenetically related. The genus Orthopoxvirus comprises camelpox, cowpox, ectromelia, MKPX, racoonpox, skunkpox, taterapox, Uasin Gishu (poxvirus of Horse), vaccinia, variola and volepox. Many poxviruses are associated with a specific vertebrate species, which indicates that the transmission of these viruses occurs preferentially among a specific vertebrate species. Although accidental transmission into a different vertebrate species can occur, there was no resultant clinicopathological condition noted in the infected host to be further maintained in this 'aberrant' species.[8] Vaccinia virus exists in nature and is commonly associated with outbreaks associated with cattle in South America, India, and other areas. Cowpox virus infects humans and infections are often noted in Europe. Variola virus is a virus which only infects humans and the Vaccinia virus is a vaccine strain used to treat smallpox. Vaccinia virus has originated in the 18th century from an unknown vertebrate species. Cowpox is a rodent virus that may infect cats, cows and zoo animals and could transmit infection to humans.

Molecular virology of monkeypox

Recent advances in molecular biology and genomics have improved our understanding of viral infection and replication mechanisms. MKPXV has a relatively large genome of about 196,858 base pairs, encoding 190 open reading frames, which constitute the bulk of the material needed for viral replication in cell cytoplasm.[4] Viral entry into cells is dependent on cell type and viral strain, and occur after an initial attachment to cell surface through interactions between multiple viral ligands and cell surface receptors[5] such as chondroitin sulphate[6] or heparan sulphate.[7,8] Subsequent crossing of cell membrane is mediated by a viral fusion event with cell membrane under neutral pH conditions,[9] or by endosomal uptake through a macropinocytosis-like mechanism that involves actin[10,11] and low pH-dependent steps.[12] Once in the cell cytoplasm, the virus releases prepackaged viral proteins and enzymatic factors that disable cell defences and stimulate expression of early genes.[13-15]

Synthesis of early proteins promotes further uncoating, DNA replication and production of intermediate transcription factors. Intermediate genes are transcribed and translated to induce the expression of late genes that function mainly as structural proteins, enzymes and early transcription factors. Eventually, membrane structures will appear and unit virion genomes processed from DNA concatemers are assembled into nascent virions that contain all enzymes, factors, and genetic information needed for a new infectious cycle. The detailed available information about viral gene functions and its programmed expression during infection exceeds current knowledge of corresponding events in the host. Furthermore, although poxviruses are considered one of the most self-sufficient viral families, they remain unable to reproduce in extracellular environment and known to have limited host range, which suggest dependence on host elements.[16,17] Therefore, identification of these specific host elements and pathways that are essential for viral replication will enrich our knowledge of host response to viral infection, and may prove valuable in identifying potential targets for antiviral therapies.

Microarrays have been used in genome exploration and profiling with a special focus on understanding dynamics of viral gene expression and pathogenesis.[18,19] However, a number of works employed this tool in examining host response to infections with poxviruses generally,[20-22] and more specifically in the case of MKPXV. Since combining microarray technology with modern data mining tools allows further information extraction at genome-wide levels, we used whole genome rhesus macaque microarrays in combination with ingenuity pathways analysis to investigate the effect of MKPXV infection on host *Maccaca mulata* kidney epithelial cells transcriptome and address gaps in host response during MKPXV infection. Functional and canonical pathway analysis of differentially expressed genes at 3 and 7 h postinfection (hpi) time points validated many of the known host gene responses to poxvirus infection and introduced new sets of interesting functions and pathways in areas of cell death and apoptosis, actin dynamics, ion channels and transport and cell cycle regulation.

HISTORICAL PERSPECTIVE OF MONKEYPOX VIRUS

The first known human case occurred in the Equateur province of Zaire (now known as the DRC) when a 9-year-old boy developed a smallpox-like illness, which was eventually confirmed as human MKPX by the World Health Organisation[1,8] Retrospectively, similar cases occurring in 1970–1971 from the Ivory Coast, Liberia, Nigeria and Sierra Leone were attributed to MKPX infection [Figure 1].

MKPX was limited to the rainforests of central and western Africa until 2003, when the first cases in the Western Hemisphere were reported. In late spring 2003, multiple

persons were identified in the Midwestern United States who had developed fever, rash, respiratory symptoms and lymphadenopathy following exposure to ill pet prairie dogs (*Cynomys* species) infected with the MKPXV.[2,9]

The West African virus causes many fewer cases, and the cases are less severe with no deaths reported to date. The central African strain has caused thousands infections per year, most reported from DRC. The mortality rate is 11% in unvaccinated individuals. Epidemics of MKPX in the DRC in 1996–1998 resulted in about 400 cases of the disease. The first wave of these epidemics lasted from February to August 1996 and involved 89 cases of clinical disease with six deaths. A follow-up investigation of MKPX in the area in February 1997, which included a hut-by-hut search for active cases in 12 villages, gave evidence that up to 73% of MKPX cases resulted from the secondary human-to-human transmission. Furthermore, three of the deaths were in children <3 years old, and a large proportion of cases were in persons <15 years old. MKPXV is, therefore, a human pathogen that can cause fatal illness, spread from person-to-person, and cause outbreaks of disease in susceptible populations. Till date, the spread has been limited, but the potential for wider spread exits if the virus mutates so that it is more readily transmissible from person to person.[9]

Monkeypox in the United States

An outbreak of MKPXV occurred in the Midwestern United States in 2003.[9] The virus was imported with a shipment from Ghana of more than 700 squirrels and rodents that included Gambian giant rats, rope squirrels, brushtail porcupines, tree squirrels, striped mice and dormice. These animals, at least some of which were infected with MKPX, were intended as pets and were distributed to many states. One such transfer of some Gambian giant rats and dormice went to a facility in Illinois where they were housed in the vicinity of U. S. prairie dogs that were also intended as pets. The prairie dogs became infected by the virus and were subsequently distributed in seven states including Illinois.[9] There were a total of 47 confirmed and probable cases in six states, 18 of whom were hospitalised. Half of the cases were confirmed by laboratory testing. There were no deaths from this West African strain of MKPX, which as described causes a milder illness in humans than does the Central African strain. To prevent the continuing spread of MKPX in this epidemic, 30 persons were immunised with the smallpox vaccine. Those vaccinated included veterinarians, health-care workers, laboratory workers and household contacts of patients. One vaccinee, who reported a rash, was confirmed as having MKPX.[10]

GLOBAL EPIDEMIOLOGY AND GEOGRAPHICAL DISTRIBUTION

Monkeypox in Africa

MKPX has presumably occurred in sub-Saharan Africa for thousands of years, ever since humans acquired the virus through direct contact with infected animals. Animal field collections and virological analyses have revealed that squirrels and other small mammals have been serologically tested and found to be positive to MKPXV; a Funisciurus squirrel from DRC was found to have live MKPXV.[1] MKPX was not recognised as a distinct disease until 1970 when the elimination of smallpox from Zaire (the present DRC) revealed the continued occurrence of a smallpox-like illness in rural areas. Widespread vaccination in central Africa during the global eradication campaign presumably caused a temporary reduction in the incidence of human MKPX, but the absence of immunity in the generation born since that time and the increased dependence on hunting for food in areas devastated by civil war have resulted in the reemergence of the disease

Initial epidemiological studies conducted during 1970–1979 detected a total of 47 cases of human MKPX near rainforests of sub-Saharan Africa, of which 38 occurred in the DRC and the remainder in Cameroon, the Central African Republic, Gabon, Cote d'Ivoire, Liberia, Nigeria and Sierra Leone.[2,3] All cases in the DRC occurred in areas bordering tropical rainforests and appeared to be associated with animal contact. Seven of the 47 reported infections were fatal. The secondary transmission was determined to be the most likely cause of infection in four cases, with secondary attack rates of 7.5% among close family members living in the same household and 3.3% among all susceptible contacts. Since 1980, the vast majority of cases have continued to be reported from the DRC.[23]

To determine whether MKPX had the potential to emerge from central Africa and occupy the niche vacated by smallpox, the World Health Organisation conducted an active surveillance programme from 1981 through 1986 in the DRC, where 338 of the 404 recognised cases in Africa occurred during 1970–1986.[4,23] An animal source of infection was suspected in 245 of the 338 cases, and secondary transmission from a human source was presumed in the remaining 93 cases. The longest documented chain of infection consisted of only four generations of person-to-person transmission, indicating that MKPXV had little potential for epidemic spread.[5,23] Serological surveys involving vaccine-naive children that were undertaken during this period found that 12%–15% of participating children had antibodies against MKPV,

but most did not have a history of compatible illness, suggesting that subclinical infection also occurred.[4,24]

Since the end of the World Health Organisation surveillance programme in 1986, to the best of our knowledge, only a handful of articles in the medical literature have described the continuing occurrence of human MKPX. During 1986–1992, only 13 cases were reported in the literature, and none were reported during 1993–1995.[6] However, in 1996–1997, more than 500 suspected cases of MKPX were reported in Kasai-Oriental province, DRC.[6,7,24] Only a small number of these cases were laboratory confirmed, and in contrast to the findings of the earlier World Health Organisation study, the percentage of secondary cases was much higher (78%) and the fatality rate much lower (1%–5%), suggesting that the great majority were actually cases of varicella. No reports of new suspected MKPX cases were published until 2001, when 31 patients with MKPX in seven separate disease clusters were described in Equateur province, DRC.[24]

Despite political instability and the consequent lack of resources, local health-care workers in the DRC continue to perform passive disease surveillance. Their reports indicate that human MKPX is occurring more frequently than the few published articles would suggest.[8] Between 1 January 1998 and 31 December 2002, a total of 1265 cases were reported to the DRC Ministry of Health, with specimens collected in 215 cases. Of these 215 cases, PCR and virus culture revealed that 88 were due to MKPXV. An active disease surveillance system is currently being established in Kasai-Oriental province, DRC, which promises to provide more-extensive and reliable data on the disease

International

This condition is rare and only known to be indigenous to the rainforests of western and central Africa. It was first recognised in humans in 1970 after the eradication of smallpox, possibly due to the subsequent unmasking of the infection. Surveillance reports from 1981 to 1986 documented 338 cases in the DRC (out of a 1982 estimated population of 5 million). In the 1996–1997 outbreaks in the DRC, the attack rate was 22 cases/1000 population. MKPX in endemic in highly forested regions of DRC. Sporadic occurrences of disease are reported in neighbouring countries. In 2003, 11 cases and 1 death were reported from the DRC and 10 cases with no deaths were reported from Sudan in 2005.[23,25,26] Human case of MKPX was reported in Sierra Leone in 2014 and 2017.[26]

In 2009, interethnic violence in Northwestern DRC led to an influx of refugees into the Republic of the Congo. The United Nations International Children's Emergency Fund sponsored a programme of intensive community education in the refugee settlements that included modules on MKPX recognition and prevention, which resulted in the identification of 10 suspected cases of MKPX. Seven of these 10 cases were tested and two were found to be positive by PCR assays.[22,27]

Conventionally, MKPXV is found in the tropical rainforests of countries in western and central Africa, most notably the DRC, but its range may be expanding. In 2003, MKPXV was imported into the USA in a shipment of rodents destined for the pet trade, and in 2005, an outbreak was recorded in southern Sudan.[20] Some studies on animal field collections have found that squirrels and other small mammals have been serologically positive to MKPXV; a Funisciurus squirrel from DRC was found to have live MKPV.[27]

Recent outbreak of monkeypox in Nigeria

On 27th October 2017, the Federal Government of Nigeria confirmed six cases of MKPX. The cases are amongst those sent to the World Health Organisation's laboratory in Dakar, Senegal, a statement by the Ministry of Health.[28] The Nigerian Minister of State for Health said two cases each were confirmed in Bayelsa and Akwa Ibom States, one each in Enugu State and the Abuja. They bring to nine the total number of MKPX cases so far confirmed in Nigeria. Three MKPX patients had earlier been confirmed on October 16, 2017. Meanwhile, there are 94 suspected cases reported from 11 states, namely, Akwa Ibom, Bayelsa, Cross River, Delta, Ekiti, Enugu, Imo, Lagos, Nasarawa, Niger, Rivers and the Federal Capital Territory.[28]

A total of 228 suspected MKPX cases were reported from 24 States and the FCT as at 25th February, 2018. Out of this, 89 cases have been confirmed in 15 States.[28] A total of six deaths have been recorded since the outbreak, four of which are in patients with background immunosuppression. Clustering of cases was revealed in Bayelsa, Rivers and Imo States but no evidence of epidemiological linkages across States was revealed.[28] Genetic sequencing suggests multiple sources of introduction of MKPXV into the human population. The male-to-female ratio for confirmed cases is 2.5:1.[28]

The Nigerian health minister said the new patients were already being managed by public health authorities and had been receiving appropriate clinical care since onset of the illness. He said the Federal Ministry of Health, through the disease control office, was in contact with all state

epidemiology teams, as well as the health facilities providing clinical care to both suspected and confirmed cases.[28]

State Commissioners of Health had been advised to place all health-care facilities, disease surveillance and notification officers on alert, to ensure early case detection, reporting and effective treatment. In addition, the Nigerian Centre for Disease Control is leading a national-level emergency operations centre with support from development partners.[28]

DIFFERENTIAL DIAGNOSIS OF DISEASES WITH SIMILAR SYMPTOMS WITH MONKEYPOX

As the clinical picture of MKPX is very similar to that of chickenpox and that of smallpox, definitive diagnosis is key to keeping natural disease under control or in the early detection of a potential bioterrorism event. The evaluation criteria in the differential diagnosis for patients with MKPX, chickenpox or smallpox are shown in Table 1. Although diseases such as orf and bovine stomatitis (which are caused by parapoxviruses) can produce localised skin lesions similar to those seen in the US MKPX outbreak, they can be easily distinguished from orthopoxviruses by electron microscopy and molecular diagnostics as well. Once the disease agent is identified, quarantine and immediate ring vaccination are the only effective public health protective procedures, because there is no effective, licenced antiviral therapy for MKPX. Given the ease of transmission through direct contact, specimens such as scab or other cutaneous tissues should be handled with care and collected aseptically with respiratory precautions.

Although clinical characteristics can be useful in distinguishing poxvirus infections from other causes of vesiculopustular rashes, laboratory confirmation is required for a definitive diagnosis. The various laboratory diagnostic assays for MKPX include virus isolation and electron microscopy, PCR, IgM and IgG enzyme-linked immunosorbent assay (ELISA), immunofluorescent antibody assay and histopathologic analysis. Unfortunately, many of these methods are relatively non-specific and are unable to differentiate MKPXV infection from infection with other poxviruses. For example, histologically, the lesions of MKPX are similar to other viral exanthems (such as those due to variola, cowpox, varicella-zoster and herpes simplex viruses) and include ballooning degeneration of keratinocytes, prominent spongiosis, dermal oedema and acute inflammation.[23] However, immunohistochemistry analysis, including the use of either polyclonal or monoclonal antibodies against all orthopoxviruses, can differentiate between a herpes virus and poxvirus infection. Electron microscopy has often played a major role in viral diagnosis in the past.[24] Similarly, if available, electron microscopy can be a first-line method for laboratory diagnosis of poxvirus infections and may provide one of the first clues to the cause of an unknown rash illness. Characteristic poxvirus virions showing the typical morphology (i.e., brick shape with lateral bodies and a central core) would be expected to be observed under electron microscopy.

For example, during the recent US outbreak of MKPX, lesions viewed using electron microscopy showed keratinocytes with large numbers of mature virons, as well as immature virons in the process of assembly (also known as "viral factories") within the cytoplasm.[23,24] This method, however, cannot differentiate orthopoxvirus species. Virus isolation (which can be accomplished by growing the virus in mammalian cell culture) and characterisation by various PCR techniques, followed by restriction fragment–length polymorphism analysis or sequencing of amplicons, are often considered to being definitive for the identification of MKPXV.[25] In addition, the availability of various real-time PCR assays that use panorthopoxvirus or MKPXV-specific targets has increased in recent years.[26,27] A DNA oligonucleotide microarray with the TNF receptor gene *crmB* has also been developed as another rapid method for species-specific detection of orthopoxviruses.[27]

Table 1: Evaluation criteria for the differential diagnosis of patients with Monkeypox, smallpox, and chickenpox

Variable	Monkeypox	Smallpox	Chickpox
Incubation period (days)	7-17	7-17	12-14
Prodrome period (days)	1-4	2-4	0-2
Symptoms			
Fever (Severity)	Moderate	Severe	Mild or none
Malaise (Severity)	Moderate	Moderate	Mild
Headache (Severity)	Moderate	Severe	Mild
Lymphadenopathy (Severity)	Moderate	None	None
Lesions			
Depth (diameter in mm)	Superficial to deep (4-6)	Deep (4-6)	Superficial (2-4)
Distribution	Centrifugal (mainly)	Centrifugal	Centripetal
Evaluation	Homogenous rash	Homogenous rash	Heterogenous rash
Time to desquamation (days)	14-21	14-21	6-14
Frequency of lesions on palms or soles of feet	Common	Common	Rare

Signs and symptoms of the diseases are not age-specific

It is important to definitively rule out smallpox at any place in the world. During active disease, laboratory confirmation can be performed by PCR analysis of vesicle fluid or scabs. Testing of patients for anti-orthopoxvirus IgM is appropriate (not anti-varicella), and the patient's specimen must be collected 5-56 days after onset of the rash. Otherwise, the test results are not interpretable. The finding of antipoxvirus antibodies in an unvaccinated individual with a history of severe illness and rash suggests a diagnosis of MKPX.

Clinical and laboratory diagnosis

For definitive diagnosis, scabs can be forwarded to a reference laboratory where electron microscopy may confirm the presence of an *Orthopoxvirus* and differentiate this virus from varicella virus. The virus can be cultured in tissue culture and identified by DNA restriction analysis.

Diagnosis

The differential diagnoses that must be considered include other rash illnesses, such as, smallpox, chickenpox, measles, bacterial skin infections, scabies, syphilis and medication-associated allergies. Lymphadenopathy during the prodromal stage of illness can be a clinical feature to distinguish it from smallpox.

MKPX can only be diagnosed definitively in the laboratory where the virus can be identified by a number of different tests:

a. Enzyme Linked ImmunoSorbent Assay (ELISA)
b. Antigen detection tests
c. PCR assay
d. Virus isolation by cell culture
e. Electron microscopy-electron microscopy reveals virions at various stages of assembly within the keratinocyte cytoplasm.

Viral culture can be attempted on any positive patient specimen, not pharyngeal swabs. Optimal specimens for poxvirus testing are lesion specimens, not throat cultures or skin biopsies.[22,28] Tissue for PCR of DNA sequence-specific for the MKPXV may be obtained. Paired sera for acute and convalescent titres may be analysed. Serum collected more than 5 days for IgM detection or serum collected more than 8 days after rash onset for IgG detection was most efficient for the detection of the MKPXV infection.[29] MKPX cases were confirmed based on virus isolation or detection of the virus by PCR from a clinical specimen (skin biopsy or throat culture). Individuals who presented with fever and rash within 21 days of exposure to MKPX and had serum positive for orthopox immunoglobulin M (IgM), but did not have culture-or PCR-positive clinical specimens, were classified as having a probable case of infection.[29,30] The most reliable clinical sign differentiating MKPX from smallpox and chickenpox is enlarged lymph nodes, especially the submental, submandibular, cervical and inguinal nodes. Regarding exanthema, non-specific lesions and inflammation of the pharyngeal, conjunctival and genital mucosae, PCR assays on these lesion specimens offer a definitive diagnosis.[28,29]

Histological examinations of papular lesions could show the presence of acanthosis, individual keratinocyte necrosis and basal vacuolisation, along with a superficial and deep perivascular, lymphohistiocytic infiltrate in the dermis. Lesions in the vesicular stage could show spongiosis with reticular and ballooning degeneration. Multinucleated epithelial giant cells can be another significant observation. Pustular lesions might show epidermal necrosis with numerous eosinophils and neutrophils, many displaying karyorrhexis. Necrosis may extend through full-thickness epidermis with sharp lateral demarcation from the adjacent intact epidermis. The associated perivascular infiltrate may include eosinophils and neutrophils in addition to lymphocytes and histiocytes and petechial lesions can reveal secondary vasculitis. Amphophilic intranuclear structures suggestive of viral inclusions may also be seen in keratinocytes.[28,29]

Immunohistochemistry staining for Orthopox viral antigens is available and can be performed in select reference laboratories. Electron microscopic observation can reveal intracytoplasmic, round-to-oval inclusions with sausage-shaped structures centrally, measuring approximately 200–300 μm. These inclusions were noted to be consistent with Orthopoxviruses, permitting differentiation from parapox and herpes viruses.[26,29]

TREATMENT

The CDC recommended smallpox vaccination within 2 weeks, ideally before 4 days, after a significant, unprotected exposure to a diseased animal or a confirmed human case.[30,31] Data from the African outbreaks suggest vaccination conferred 85% protection in close household contacts who were vaccinated 3–19 years previously. Efficacy of vaccination was noted to be prolonged with protection noted even several years after vaccination, and the incidence of complications being reduced.[8,32]

In regard to human infection with MKPXV vaccination with Vaccinia virus, there are many aspects to the risk/benefit ratio that should be considered, as well as, the potential use of pre-exposure or postexposure vaccination. Traditional smallpox vaccination is not recommended for HIV patients, but newer vaccines may be an option. Experimental antiviral

treatments are not available in endemic areas but should they be considered or evaluated further. In addition, the treatment is not devoid of side effects. These may include vomiting, neutropenia, hair loss, muscle weakness and uveitis.[32]

PREVENTION AND CONTROL

Improved infection control measures, including the regular screening, and isolation of newly infected animals will certainly help in preventing outbreaks among animals. Better hygiene habits are warranted to avoid spreading of the virus on fomites which then become a source for newer infections. Vaccination with vaccinia virus could be choice to protect animals. Because infections have been reported in Asian monkeys mixed with primates from Africa, care must be taken to house these species separately. Anyone who has been exposed to MKPXV should avoid contact with animals, particularly rodents and non-human primates, to stop transmitting the virus.[32]

During an outbreak, the MKPX viral spread may be controlled by quarantining (at least for 6 weeks from the date of the last exposure) the infected animals and tracing of their contacts. Areas where these animals have been kept should be cleaned and disinfected thoroughly adherence to specific instructions from the state or local health department. The following may be observed as follows:

a. Use personal protective equipment when caring for MKPX patients
b. Avoiding close contact with infected people
c. Isolation of infected patients from others who could be at risk for infection
d. Avoid contact with animals that could harbour the virus including animals that are sick or that have been found dead in areas where MKPX occur
e. Cooking of meat and meat products thoroughly before eating
f. Washing hands with soap and running water frequently and thoroughly
g. Vaccination against smallpox has been proven to be 85% effective in preventing MKPX.

CONCLUSION

MKPX occurs mainly in the jungles of central and western Africa. The disease, unlike smallpox, is a typical zoonosis in that most cases occur as a result of direct contact with an infected animal. The symptoms of the disease in humans can be very similar to those of smallpox, chickenpox or other causes of vesiculopustular rash; therefore, accurate and rapid laboratory diagnostics are paramount in controlling an outbreak. The similarity of African MKPX cases to smallpox cases, as well as the growing lack of immunity in the population since the discontinuation of routine smallpox vaccination, has led to the concern that MKPXV might be used as a bioweapon. For these reasons, MKPXV, along with Variola virus and other poxviruses, has been placed on the National Institutes of Health's highest category threat list (National Institute of Allergy and Infectious Diseases Category A priority pathogen) and is considered to be a "select

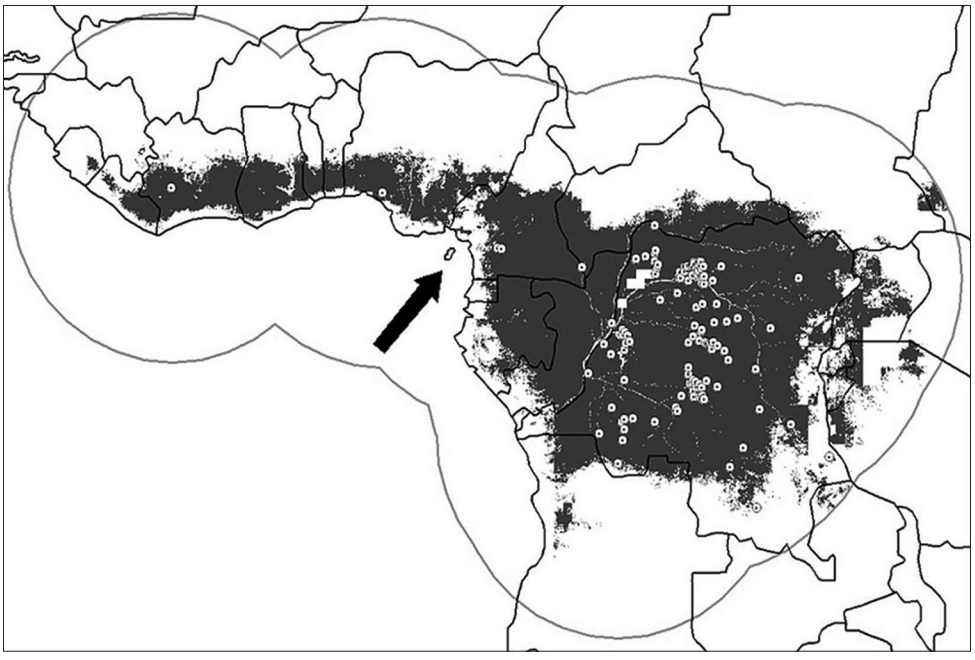

Figure 1: Geographical distribution Monkeypox known occurrence points (dotted circles), predicted potential geographic distribution (gray shading)

agent" (defined as bacteria, viruses, toxins, rickettsia and fungi that pose a potential threat to public health or welfare) by the CDC. Although not a result of bioterrorism, the introduction of a disease such as MKPX into a new, previously disease-free region of the world, as happened with the 2003 MKPX outbreak in the United States, can cause substantial alarm and even fear. This event has brought attention to the issues related to trade of exotic pets and has further raised concerns pertaining to the increasing global transport of wild animals and other potential vectors of infectious diseases once thought to be geographically restricted and not a concern for the United States. In November 2003, the CDC and the Food and Drug Administration issued the interim final rule to prohibit the import, capture, transport, sale, barter, exchange, distribution and release of African rodents, prairie dogs and certain other animals into the environment, to prevent the spread of MKPX in the United States.

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Conflicts of interest

There are no conflicts of interest.

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