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REVIEW

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A review of the monkeypox virus and a recent outbreak of skin rash disease in Nigeria

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Since the eradication of smallpox approximately 39 years ago, monkeypox virus remains the most pathogenic poxvirus, being mainly restricted to Central and West Africa. Before 1970, there were no reports of human monkeypox in Nigeria, while between 1971 and 1978 there were three cases, with none having been reported thereafter. However, in September 2017, a case of contagious skin rash disease, typical of monkeypox, was observed in an 11-year-old boy from the southern part of the country and confirmed to be associated with the monkeypox virus. This large outbreak consisted of 262 suspected, 115 confirmed cases, and 7 mortalities across 26 states and the Federal Capital Territory (FCT), Abuja. The aim of this manuscript is to provide an updated, comprehensive, and timely review of monkeypox, an important emerging infection in Nigeria. Monkeypox is now a major threat to global health security, requiring an urgent multidisciplinary approach involving veterinarians, physicians, virologists, and public health experts to fast-track the development of diagnostic assays, vaccines, antivirals, and other control strategies.

KEYWORDS
Africa, antipoxvirus agents, epidemiology, infectious diseases, monkeypox, Nigeria, outbreak, poxviruses, re-emerging infection, zoonotic

1 | INTRODUCTION

Viruses continue to be responsible for a large number of emerging and re-emerging infections of medical importance as well as a wide range of human and animal infectious diseases. They proportionally pose a much greater threat to global public health than a century ago.[1] Viruses cause the most feared and devastating human diseases, their ability to spread rapidly making them major contributors to global infectious disease morbidity and mortality.[2,3] In addition, a number of viruses have a dual use as biological weapons and tools of mass destruction.[4-7] As the world celebrates four decades of smallpox eradication, Nigeria began to experience a recent outbreak of severe skin rash syndrome that mimics a form of varicella zoster and smallpox, with monkeypox virus (MPXV) being the etiologic agent.[8]

As half of the world's population has no immunity against orthopoxviruses,[9] there is a high tendency for poxviruses to emerge outside their normal ecological range through transmission to naive population.[10] This is evidenced by the increasing magnitude and frequency of epidemic outbreaks of other orthopoxvirus infections, such as cowpox and buffalopox,[11] with the more established cases of human–to-human transmission of monkeypox viruses being further validated by the current outbreak in Nigeria.[12,13] It is also pertinent to consider environmental changes, human behavior, socioeconomic and demographic phenomena, travel and commerce, food production, health care, microbial adaptation, and public health measures as important drivers that need to be considered to change the dynamics of this infection. The manuscript provides a comprehensive review of the disease in Nigeria, the most recent information about monkeypox

virus biology as well as its virus-host interaction, epidemiology, diagnosis, chemotherapy, prevention, and control strategies.

2 | BIOLOGY OF POXVIRUSES: TAXONOMY AND HISTORICAL BACKGROUND

Poxviruses are a unique, complex, and diverse group of large DNA viruses that synthesize both their RNA and DNA in the cytoplasm of infected cells. The Poxviridae family contains many clinically important viruses that are categorized into two large subfamilies and 16 genera (Figure 1).[14] The two subfamilies are based on host range, these being *Chordopoxvirinae*, which infects vertebrates, and *Entomopoxvirinae*, which infect insects. In the former group, a number of viruses (eg, monkeypox, cowpox, and tanapox) infect birds and animals, such as monkeys and cows, and occasionally transmit and cause diseases in humans.[15] MPXV was discovered in 1958, named in 1971, and 3 years later was assigned under the genus *Orthopoxvirus* and *Poxviridae* family. In 1978, MPXV became a full member of the *Poxviridae* family, *Chordopoxvirinae* subfamily and genus *Orthopoxvirus*,[16] and remains the most pathogenic species since the eradication of the smallpox virus.

MPXV is an enveloped double-stranded DNA virus with an approximate genome size of 190 kb, and is enclosed in a slightly pleomorphic dumbbell-shaped core of 140 to 260 nm diameter, giving a brick-shaped virion. The genome has closed hairpins on both ends and several open reading frames (ORF) that cover more than 180 nucleotide size.[17,18] There is a highly conserved central coding region of approximately 56 to 120 kb that is flanked by variable regions and terminal repeats, these containing four additional ORFs that are mainly involved in immunomodulation for host range determination and pathogenicity.[17-20] MPXV replicates within the cytoplasm of infected cells rather than in the nucleus, in contrast to many DNA viruses, as they can produce the required proteins for both transcription and replication. The virus falls into two distinct clades, based on genetic, geographic and phenotypic variation, these being the West African and the Congo Basin groups, with defined epidemiological and clinical differences, those assigned to the latter being the most virulent.[21]

3 | EPIDEMIOLOGY

Unlike the variola virus, the causative agent of smallpox, which is the only human pathogen with no known animal reservoirs yet, MPXV has a wide range of permissible animal reservoir(s).[22-24] Human monkeypox (MPX) is a sporadic smallpox-like, rare, zoonotic disease that was first discovered in captive monkeys in Denmark in 1958.[25,26] Human infection with monkeypox virus was first described

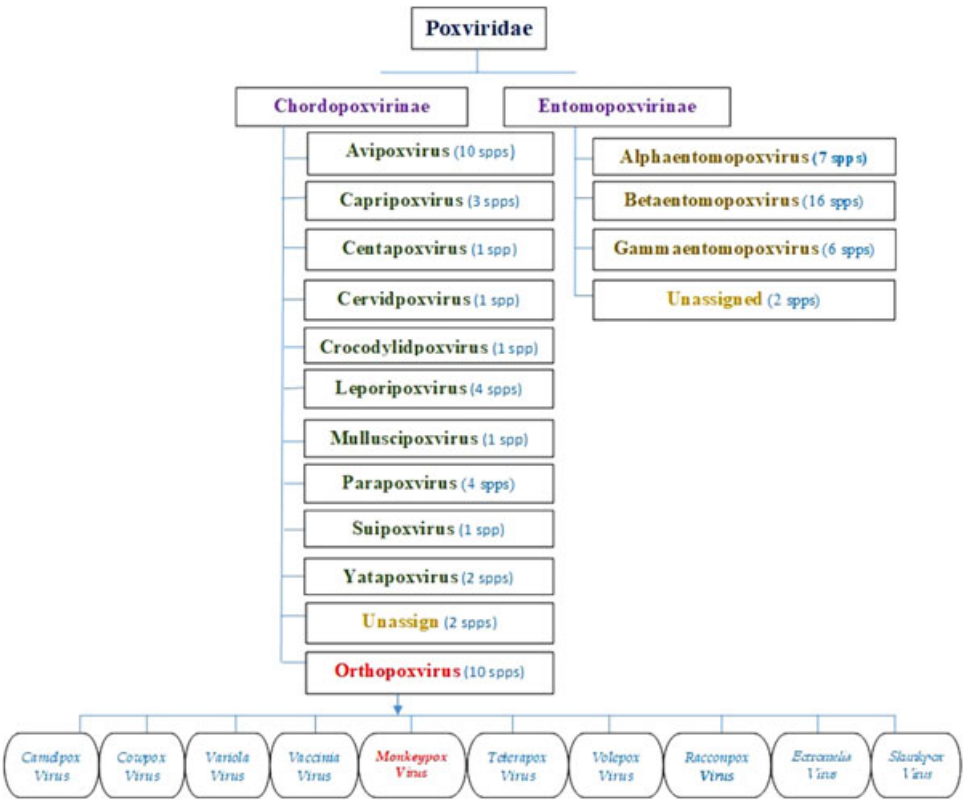

FIGURE 1 Taxonomy of poxviruses: the figure indicates the family, two subfamilies with emphasis on *Chordopoxvirinae* subfamily, and the 12 genera. Monkeypox virus is a member of the genus *Orthopoxvirus* together with nine other important human and animal viruses, including variola virus, vaccinia virus, cowpox virus, camelpox virus, tetrapox virus, volepox virus, racconpox virus, ectromelia virus, and skunkpox virus

TABLE 1 Summary of confirmed human monkeypox in Nigeria from 1971 to 2018

Y	Zone	Affected states	Cases	Death	Reference
1971	SE	Abia	02	0	Foster et al[29]
					Durski et al[34]
1978	SW	Oyo	01	0	Durski et al[34]
2017-2018	NC	FCT, Nassarawa, Benue, Plateau	115[a]	07[a]	NCDC[49]
	SE	Abia, Enugu, Imo, Ebonyi, Anambra			Durski et al[34]
	SW	Ekiti, Lagos, Oyo			
	SS	Akwa Ibom, Bayelsa, Edo, Delta, Cross River, Rivers			
Total			118	07	

Abbreviations: FCT, Federal Capital Territory; NC, North Central; SE, South East; SW, South West; SS, South South;
[a]The total confirmed cases and mortalities in 2017-2018 outbreak were 115 and 07, respectively, as of 15 September 2018.

in Central Africa in 1970 in a 9–month-old child from Zaire (now the Democratic Republic of the Congo).[27-31] Since then, the MPXV has become the most pathogenic orthopoxvirus and is now endemic in the most forested regions of Central Africa, mainly the Democratic Republic of the Congo, where it is considered a reportable disease as well as in some parts of West Africa.[32] Transmission to humans is primarily by exposure to animal reservoirs (primary zoonotic transmission), such as squirrels of the genera *Funisciurus* and *Heliosciurus*.[33]

Human monkeypox is frequent in villages where there is a high possibility of contact with infected animals. As shown in Table 2, from 1970 to 2018, cases were reported in Cameroon, Côte d'Ivoire, Central African Republic, the Democratic Republic of the Congo, Gabon, Nigeria, Sierra Leone and Sudan.[34] Serologic studies have shown that monkeys from Africa have orthopoxvirus antibodies, while natural cases of MPXV are yet to be documented in wild-living primates.[35,36] It was reported that monkeypox virus neutralizing antibodies have been detected in the domestic pig (*Sus scrofa*), Gambian rat (*Cricetomys emini*), elephant shrew (*Petrodromus tetradactylus*), Thomas's tree/rope squirrel (*Funisciurus anerythrus*), Kuhl's tree squirrel (*Funisciurus congicus*), and sun squirrel (*Heliosciurus rufobrachium*),[22] suggesting the role of wildlife in zoonotic transmission.[23,24,37]

Furthermore, sera obtained from 55 monkeys (species unknown) in Nigeria were reported seronegative.[38] Hunting and butchering bushmeat were among the risk activities for primary zoonotic transmission.[22,39,40] Human–to-human transmission (especially with the West African or the Congo Basin clades) was reported by direct inoculation via contact with body fluids, such as blood, respiratory droplets, saliva or lesion exudate and crust, and was associated with a more pronounced illness.[41] Nigeria experienced two outbreaks of human monkeypox, the first being in 1971 and the second in 1978, where three confirmed cases were reported.[42] Other outbreaks occurred in Sudan in 2005 (19 cases), the Democratic Republic of the Congo in 2009 (2 cases), and recently in the Central African Republic in 2016-2017 (31 cases).[34,43] In the western hemisphere, an outbreak of febrile illness with vesiculopustular eruptions was reported in the United States of America in 2003, where 72 confirmed or suspected cases were documented, which shows the propensity for MPXV transmission to naïve population and its ability to emerge outside its normal ecological range.[10] Similarly, there is documented evidence about the existence of the virus in wild animals in Uganda, East Africa, and Zambia in Southern Africa.[44,45] Human monkeypox has a predilection for males when compared to females, due possibly to their occupational tendencies, with poor housing structure as an important factor for transmission. There is a high fatality rate in young children,[46] with case fatalities being 10% to 11%, depending on the vaccination status (for smallpox) and age at presentation.[47]

TABLE 2 Countries with reported evidence of human or animal monkeypox in Africa (1970-2018)

Countries	Host	Reference
Cameroon	Human and animal	Durski et al[34]
CAR	Human and animal	Durski et al[34]
Cote'd Ivoire	Human and animal	Durski et al[34]
		Radonić et al[28]
DRC	Human and animal	Durski et al[34]
		Nolen et al[32]
Gabon	Human	Meyer et al[39]
		Durski et al[34]
Ghana	Animal	Reynolds et al[42]
Liberia	Human	Durski et al[34]
Nigeria	Human	Durski et al[34]
Sierra Leone	Human	Durski et al[34]
Sudan	Human and animal	Nakazawa et al[50]
		Durski et al[34]
Uganda	Animal	Salzer et al[44]
Zambia	Animal	Orba et al[45]

Abbreviations: CAR, Central Africa Republic; DRC, The Democratic Republic of the Congo.

4 | MOST RECENT OUTBREAK IN NIGERIA

The most recent outbreak started in September 2017 in the Yenagoa Local Government Area of Bayelsa State in the southern part of Nigeria,[48] this being a riverine area, and home to the Edumanom Forest Reserve where chimpanzees were last seen in June 2008. The area is not in close proximity to the Democratic Republic of the Congo, which is the endemic zone of monkeypox, but proximate to Abia State where the first case was identified in Nigeria in 1971.[29] The disease was first suspected in an 11-year old boy who presented with fever, headache, malaise, sore throat and generalized well-circumscribed papulopustular rashes that eventually ulcerated, with

crust and scab formation.[48,49] Five of his siblings in the same household developed similar clinical signs and symptoms.[53] Although the index case and two of the siblings had reported contact with a monkey in their neighborhood, it was very difficult to ascertain if that monkey was the source of infection,[53] especially as it had no history of the illness. Thereafter, 262 suspected and 115 confirmed cases, with seven mortalities, were reported from 26 states and the FCT (Figure 2 and Table 1).[34,43,48,49] The infected persons were mostly between the ages of 20 and 39 years (median age 30 years) with a male–to-female ratio of 2.5 to 1, and of the seven patients who succumbed to the disease, four had immunosuppression.[49] Laboratory investigations established a very close relationship with the two viral strains that were responsible for the previous outbreaks in the country. In addition, nine of the MPXV negative swab samples tested positive for varicella zoster virus.[48] It was suggested that the index case of this outbreak was not imported, and that the cases were rather a spillover from the reservoir hosts.[43] This may have occurred following civil conflict and displacements in the area, with the movement of individuals to more heavily forested areas exposing them to the interaction with wildlife, thereby allowing the movement of the virus, similar to the outbreaks in the Democratic Republic of the Congo and South Sudan.[50-52] So far, this is the largest outbreak caused by the West African clade, and further investigation measures are in place to improve the existing knowledge to ensure effective prevention and control strategies.[53] A summary of cases in Nigeria from 1971 to 2018 is depicted in Table 1.

5 | DIAGNOSIS: CLINICAL PRESENTATION

MPXV is the most notable orthopoxvirus affecting humans since the eradication of smallpox.[54] The pathogenesis and clinical picture of the human MPX (Figure 3) largely resemble that of a discrete, ordinary smallpox, with an incubation period of 7 to 17 days, an initial febrile prodromal period of 1 to 4 days, and a rash period of 14-28 days. MPXV and smallpox share similar appearance, distribution, and progression of lesions.[51,52,54] The characteristic features include a prodrome of fever, headache, muscle aches, backache, and lymphadenopathy, later followed by generalized well-circumscribed rashes of typical centrifugal pattern that progress through macular, papular, vesicular, and pustular phases (Figure 4).[53,55] A second febrile period occurs when the lesions become pustular, and is often associated with a deteriorating condition of the patient.[56] A more severe disease is associated with pronounced illness, high viremia, and death, as observed following direct human–to-human transmission, however, without sustained infection.[21,27,57] Vaccination against smallpox offers some form of protection, with severe complications being observed among the unvaccinated (74%) more than the vaccinated group (39.5%).[52]

6 | COMPLICATIONS

Bronchopneumonia, shock secondary to diarrhea, vomiting, corneal scarring leading to permanent blindness as well as encephalitis,

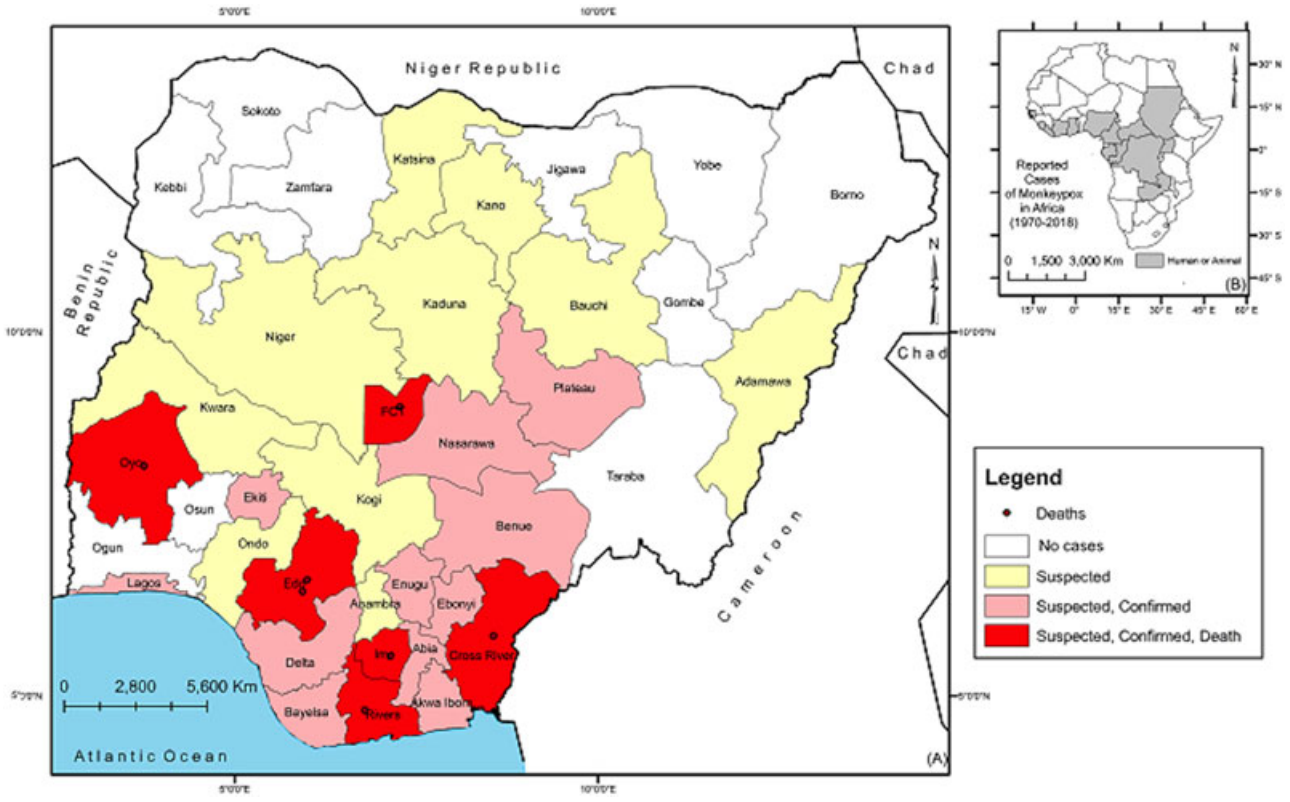

FIGURE 2 Distribution of suspected and confirmed human monkeypox in Nigeria as of 15 September 2018 including seven mortalities. Confirmed cases were from Abia, Benue, Akwa Ibom, Bayelsa, Cross River, Delta, FCT, Edo, Ekiti, Enugu, Imo, Lagos, Nassarawa, and Oyo while seven people died from Bayelsa, Ekiti, Cross River, Imo, Rivers States, and the Federal Capital Territory

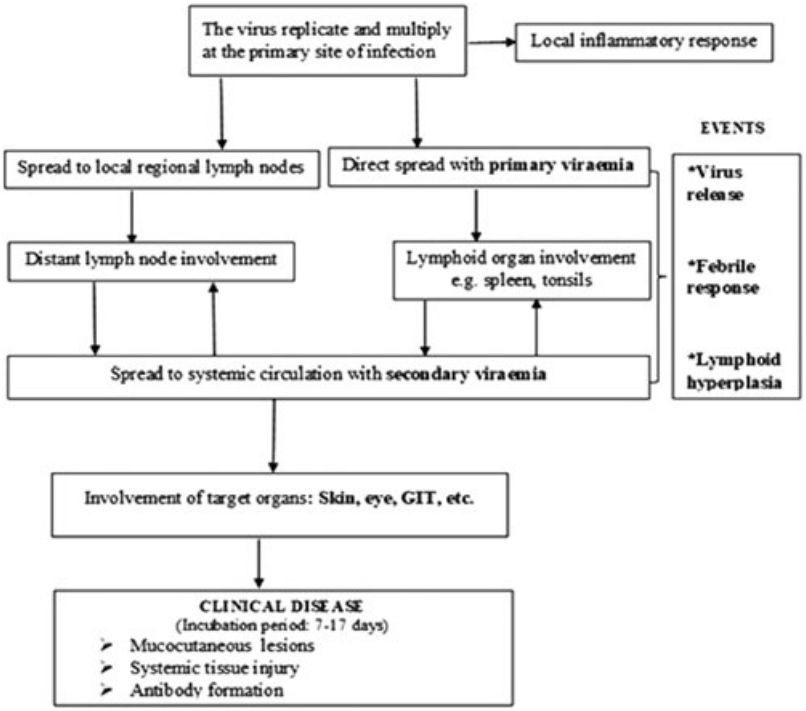

FIGURE 3 Schematic representation of pathogenesis of monkeypox virus infection in humans

especially in patients with secondary bacterial infection, and septicemia are among the documented complications, with pitted scarring of the skin as a long-term sequel.[47,58]

7 | LABORATORY DIAGNOSIS

The diagnosis of human monkeypox is mainly clinical, with the typical rashes and a high index of suspicion. Despite the fact that smallpox was eradicated, severe forms of varicella and Stevens-Johnson syndrome remain subjects for deliberation. Thus, an adequate clinical history, including travel, occupation, and contact as well as a laboratory diagnosis, are essential for clinical distinction between the rashes. Viral isolation and culture, immunohistochemistry for viral antigen detection, enzyme-linked immunosorbent assay for antibodies detection (IgG and IgM), and specific viral DNA detection using polymerase chain reaction are required to establish a definitive diagnosis. In addition, any handling of suspicious infectious samples should only be conducted in a biosafety level three (BSL-3) containment laboratory. The accuracy and validity of GeneXpert were recently evaluated, suggesting its viability as a diagnostic platform that may expand and expedite current MPXV detection capabilities in endemic areas.[59]

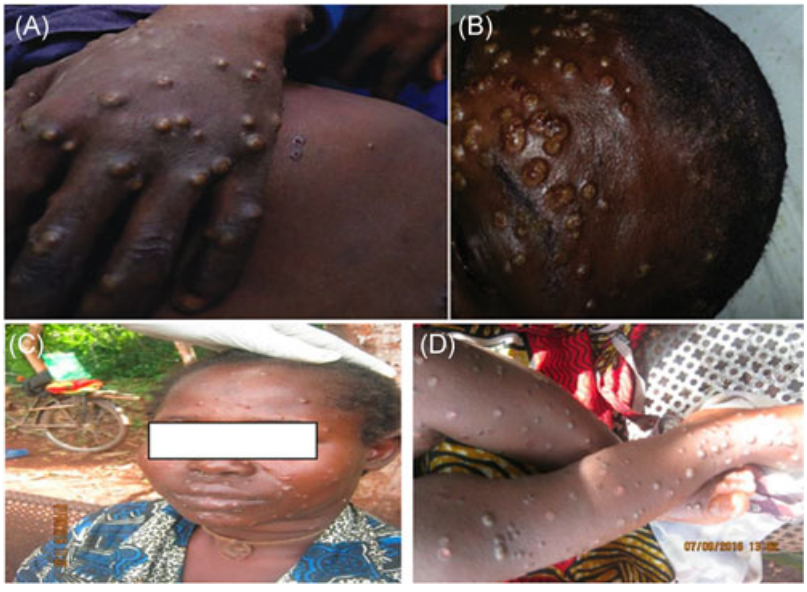

FIGURE 4 Characteristic papulopustular rash on hand (A), face (B, C), and legs (D) of patients with monkeypox. Images (A) and (B) were reproduced with permission from Yinka-Ogunleye et al[53] (published by the US Centers for Disease Control and Prevention) and images (C) and (D) were reproduced with permission from Kalthan et al[55] copyright 2018, (published by Elsevier Masson SAS). All rights reserved

8 | THERAPY AND CONTROL

Initially, treatment of monkeypox infections was mainly syndromic, as there was no clinically approved and licensed antiviral agents for its specific treatment. While still at various stages of clinical trials, four compounds (NIOCH-14, Cidofovir, CMX-001, and ST-246) may yield a good therapeutic effect.[9,52] Recently, the US Food and Drug Administration (FDA) approved in 2018 the first antipoxvirus drug intended to treat orthopoxviruses, such as smallpox and monkeypox.[60,61] This represents a long-awaited addition to disease prevention strategies that have focused on selective antiviral chemotherapy. In addition, it is a move that could halt a lethal pandemic if the virus was to be released as a bioweapon or accidentally through a laboratory-acquired infection. Tecovirimat or Arestyvir (previously ST-246) was first reported in 2005 following screening of a chemically diverse library of more than 356 240 compounds,[62-64] and was reported to be a selective and potent inhibitor of the replication of multiple orthopoxviruses.[63] The antiviral agent, tecovirimat, also known as Tpoxx, has never been tested in humans with smallpox, as the disease was declared eradicated in 1980,[65] two years after the last known and reported case of smallpox in 1978. Tecovirimat, a virion egress inhibitor, was very effective at protecting nonhuman primates challenged with variola virus (the causative agent of smallpox)[66] and MPXV[67] as well as in two animal models deliberately infected with monkeypox and rabbitpox, in accordance with the US FDA Animal Efficacy Rule.[68] It also caused no severe side effects when safety-tested in a placebo-controlled pharmacokinetic and safety trial involving 449 healthy adult human volunteers.[68] Therefore, tecovirimat is the only currently available antipoxvirus therapeutic agent, and it is stockpiled as part of the US Strategic National Stockpile for use as a defense to treat smallpox virus infections in the event of a possible bioterrorist attack.[63,69] Nevertheless, the smallpox vaccine, although with limited use due to cost and safety concerns of a live vaccinia virus vaccine, is cross protective against many orthopoxviruses, including MPXV.[34] Despite continuous and unrelenting efforts to develop an effective therapy, other public health measures, such as case isolation, contact tracing, avoiding contact with animals or materials suspected of harboring the etiologic agent, use of personal protective equipment and good hand-hygiene practices, remain the best measures for preventing and controlling human monkeypox.

9 | CONCLUSION

Since 1970, MPX cases have been reported in ten African countries with Nigeria having experienced its largest documented outbreak. Monkeypox virus remains the most pathogenic poxvirus circulating in Central Africa, with some foci in West Africa. The 2017–2018 outbreak in Nigeria suggests a spillover event from reservoir hosts in an area where civil conflict and displacements took place, presumably providing suitable reasons for movement of the virus into an area where it had previously not existed. To date, this is the most severe outbreak in West Africa, with 262 suspected and 115 confirmed cases, resulting in seven mortalities. This indicates the urgency for surveillance and the search for the source of the virus spillover. Typically, patients with human monkeypox present with constitutional symptoms of fever, headache, muscle aches and backache, followed by lymphadenopathy and well-circumscribed pustular rashes of centrifugal distribution. The recent development and license of tecovirimat as an antipoxvirus cure is an achievement in antiviral therapy. Although the vaccinia virus vaccine can protect humans against monkeypox virus infection, symptomatic management and adequate environmental public health measures provide the foremost line of care, with reduced mortality and morbidity.

At the time of this report, two cases of MPXV were separately reported in the UK for the first time, in September 2018. The first being a Nigerian resident staying at a naval base in Cornwell, and the second being a resident who had a travel history to Nigeria.[70] This represents the first appearance of MPXV as a human pathogen in Europe and its second appearance outside its endemic African region. The third case of a health care worker was diagnosed with MPXV in September 2018 following treating the second confirmed MPXV case in the UK.[71] The only other reported cases of MPXV infection in humans outside Africa occurred in the United States in 2003, where 37 were laboratory confirmed and 10 probable cases were reported.[10,72,73] Most patients were reported to have had close contact with pet prairie dogs that were infected by African rodents imported into Texas and other states within the United States in a shipment of wild animals from Ghana, West Africa.[74] In general, the recent apparent increase of monkeypox across a wide geographic area suggests the potential for its further spread, thus calls for an improved level of concern and action. The limited specific experience, surveillance capacity, laboratory capacities, disease treatment, infection control, and knowledge about the disease in the region requires further concerted global efforts to contain the disease.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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