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Review article

Emergence and public health implications of the akhmeta virus: Insights and recommendations

Olalekan John Okesanya[1], Olawunmi Blessing Amisu[2] , Emery Manirambona[3] , Jerico Bautista Ogaya[4,5,6] , William K. Chung[7] , Don Eliseo Lucero-Prisno III[8,9,10] , Bonaventure Michael Ukoaka[11] , Mohamed Mustaf Ahmed[12] , Nimat Bola Idris[13] , Inihebe Ime Okon[14] , Gilbert Eshun[15] , Cecilia Aderonke Ogunlayi[16]

1- *Department of Public Health and Maritime Transport, University of Thessaly, Volos, Greece*
2- *Department of Medical Laboratory Services, State Hospital, Ede, Osun State.*
3- *College of Medicine and Health Sciences, University of Rwanda, Kigali, Rwanda*
4- *Department of Medical Technology, Institute of Health Sciences and Nursing, Far Eastern University, Manila, Philippines*
5- *Center for University Research, University of Makati, Makati, Philippines*
6- *St. Paul University Iloilo, Iloilo City, Philippines*
7- *Department of Biology, Krieger School of Arts and Sciences, Johns Hopkins University, Baltimore, USA*
8- *Department of Global Health and Development, London School of Hygiene and Tropical Medicine, London, United Kingdom*
9- *Research and Development Office, Biliran Province State University, Naval, Leyte, Philippines*
10- *Research and Innovation Office, Southern Leyte State University, Sogod, Southern Leyte, Philippines*
11- *Department of Internal Medicine, Asokoro District Hospital, Abuja, Nigeria*
12- *Faculty of Medicine and Health Sciences, SIMAD University, Mogadishu, Somalia*
13- *Department of Public Health, Al-Hikmah University, Ilorin, Kwara State, Nigeria*
14- *Department of Research, Medical Research Circle (MedReC), Bukavu, DR Congo*
15- *Seventh Day Adventist Hospital, Agona-Asamang, Ghana*
16- *Department of Medical Laboratory Science, Neuropsychiatric Hospital, Aro, Abeokuta, Nigeria*

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ABSTRACT

Background: Global health concerns have arisen following the discovery and emergence of the akhmeta virus (AKMV) in Georgia. The first two cases of AKMV infection, a novel orthopoxvirus, in 2013, diagnosed among two cattle herders, prompted scientific research into the cause, dynamics of transmission, and clinical signs of the infection. Advancements in genomic technology, particularly regarding genomic characterization, have revealed distinct traits and potential recombination events, shedding light on this organism's evolutionary history and pathogenicity. The characteristic skin lesions and systemic signs of AKMV infections make identification and treatment difficult. An adequate understanding of the natural history and transmission mechanisms is imperative to enact strategic infection prevention measures. More so, immunization, monitoring, and early case identification, backed up by a high index of suspicion, are crucial in mitigating the progression of isolated outbreaks into large-scale epidemics. The disease management modalities must prioritize primary prevention and biohazard combat measures. Concurrently, proactive measures for the prompt development of precision antiviral agents are being instituted to abate further public health harm. To address stigma and foster inclusivity, the disease taxonomy and nomenclature for AKMV should be aligned with WHO guidelines on disease classification and terminology. Mitigating the impact of AKMV and other emerging infectious illnesses on public health requires proactive measures like vaccination, surveillance, and research into antiviral medicines. The role of relevant stakeholders, such as the government, researchers, and healthcare practitioners, is pivotal to combating the potential threat posed by the AKMV.

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* *Corresponding author:* Olawunmi Blessing Amisu
E-mail address: olawunmiblessing123@gmail.com

Introduction

The complete eradication of pathogenic microbes from the human population is unlikely. This necessitates a shift in focus towards improved preparedness for coexistence with evolving microbial threats, particularly viruses. The isolation of a new orthopoxvirus (OPXV) known as the akhmeta virus in the skin lesions of herdsmen in the Kakheti region of Akhmeta, Georgia, in 2013 marked another era of grappling with viral threats. These lesions were akin to those of cowpox virus (CPXV) infections. However, viral isolation and DNA sequencing unraveled yet another novel OPXV in samples analyzed by the U.S. centers for disease control and prevention (CDC) in Atlanta, GA, USA, and the national center for disease control and public health (NCDC) in Tbilisi, Georgia. The akhmeta virus belongs to the poxviridae family, specifically within the OPXV genus, which harbors similar viruses as cowpox, monkeypox, and smallpox. Orthopoxviruses are characterized by a characteristic clinical presentation, typically involving a rash or blisters on the skin, and are often transmitted through contact with infected animals or contaminated materials [1]. Investigations across Georgian districts starting in 2015 researched the virus's natural hosts and reservoirs. Five viral strains have been isolated from lesions and organs taken from sylvatic rodents of the genus apodemus [2]. Surveying viral reservoirs in mammalian species is crucial for understanding the virus's natural history and zoonotic potential. This knowledge can inform public health interventions in Georgia to mitigate the risk of spillover events and human infections. Genomic characterization of the AKMV has suggested a possible recombination of strains from other orthopoxvirus species. This has implications for the evolution of the viruses, their capacity to infect mammalian hosts, adaptation to new host species [2], and the risk of resistance to vaccines and antivirals. A comprehensive analysis of the akhmeta virus is necessary to guide future investigations and prevent the consequences of this novel infectious disease. This study aims to review the genetic makeup, clinical presentation, public health implications, and recommendations regarding the akhmeta virus to guide global prevention and management policies.

Case presentation and disease epidemiology

The first infectious cases of OPXV in rats were reported in Georgia in the 1980s and were endemic to southeastern Kakheti [3]. The cowpox virus was identified in 1986 from mixed tissue samples obtained from red-tailed jirds, also known as meriones libycus [4]. These isolates were identified as cowpox viruses based on their pathogenicity in rabbits, hemagglutinating activity, and distinctive pock appearance on chicken embryo chorioallantoic membranes (CAM) [4]. A 24-year-old previously healthy herd rarer who had not received the smallpox vaccination presented in June 2013 with about ten offensive but itchy sores on both hands. Before his symptoms, lesions were spotted on the cattle teats in his herd, including teat contracture that reduced milk production [4]. Two weeks into the disease, symptoms and signs of a high-grade fever (39°C), thick scars, swelling on both hands and right axillary lymphadenopathy were elicited on examination. Total leukocytosis and differential lymphocytosis were not in keeping with a bacterial infection. Symptoms and signs were suggestive; however, cutaneous anthrax was ruled out [4].

Ten days later, a 36-year-old male from the same farm reported similar symptoms. Previous medical history was insignificant, but vaccination history was the same as in the first case. Five days into the illness, lesions disappeared, but left axillary lymphadenopathy with fever was reported. Cowpox was assumed to be the origin of the patient's sickness according to their history of interaction with afflicted cows and the distinctive appearance of their lesions. A quantitative real-time polymerase-chain-reaction (RT-PCR) assay and DNA sequence analysis suggested a novel orthopoxvirus. This was the first instance of human infection with the akhmeta virus that had been reported [1]. Ecological studies conducted across settlements in Georgia investigated the transmission patterns and disease characterization of organs and skin lesions from the sylvatic rodents of the genus apodemus. Findings from these studies demonstrated the virus had a wide geographic range in Georgia [2]. A decade later, a third case of AKMV infection in humans was diagnosed retrospectively in 2023 during anthrax testing in Georgia. This was a case of another cattle owner whose clinical presentation was similar to the earlier reported index patients with hand lesions, fever, and lymphadenopathy. The patient resided over 250 km away from the incident cases. This

confirmed the assertion of a broader geographic distribution of the virus [1].

Genetic characterization of AKMV

AKMV has huge, brick-shaped, or ovoid virions with a double-stranded DNA (dsDNA) genome, similar to other orthopoxviruses [5]. The virus replicates and multiplies in the cytoplasm of the infected host cell. Its genome comprises a single linear dsDNA molecule covalently closed at both ends and ranging between 128 and 365 kbp in size. The AKMV genome codes for more than 200 genes, some of which encode proteins important in innate and adaptive host immune responses to viruses [5]. These poxvirus proteins can interfere with the detection of viral infection, alter intracellular signaling pathways, prevent transcription factors and adaptor proteins from activating, and help the latter develop evasion mechanisms [6]. The two antigenically different forms of the akhmeta virus found during infection are extracellular enveloped (EV) and mature virions (MV). A nucleoprotein core encircled by a lipid membrane with about 20 proteins makes up the more than 80 protein MV form. These key proteins carry out viral mRNA synthesis and modification. The extra membrane covering the MV form gives rise to the EV form, constituting nine different proteins: A33, A34, A36, A56, B5, E2, F12, F13, and K2 [7].

The genomic characterization of three AKMV isolates, AKMV_AKHM13-85, AKMV_AKHM13-88, and AKMV_VANI10, by the individual assembly of raw Illumina reads resulted in five continuous sequences of nucleotides (contigs) with different average coverage produced by each assembly for each isolate. Each assembly resulted in five contigs per isolate, with varying coverage, and suggested that tandem repeats are mostly responsible for these gaps. With a G + C content of 66.5%, the full genomes of AKMV_AKHM13-85 and AKMV_AKHM13-88 were 221,902 bp and 221,911 bp, respectively (Table 1). Only three single nucleotide polymorphisms (SNPs) and one six-nucleotide insertion/deletion (indel) separated these highly identical genomes [8,9]. Due to insufficient DNA, the assembled AKMV_VANI10 genome, which had a length of 217,740 bp, had two gaps filled with NNNN. In comparison to AKMV_AKHM13-88, this genome showed 2146 SNPs and 156 indels. The AKMV_AKHM13 genome's 220 putative genes were identified by gene annotation; these genes all have sequence identities with cowpox virus (CPXV) genes. The AKMV_AKHM13 inverted terminal repeats (ITRs) resembled CPXV in size and structure, featuring lengthy tandem repeat sequences surrounded by non-repetitive unique sequences. The center section of the AKMV genome, whose gene content and order were mostly conserved, showed excellent conservation compared to the genomes of CPXVs and ECTV. On the other hand, there was more variety in the terminal sections, where deletions and sequence variations were seen, especially in genes linked to virulence and host range determination. Although there were strain-dependent variances, AKMV and CPXVs shared a comparable gene complement despite these variations [10,11]. The AKMV has been genetically characterized, revealing unique genomic features compared to single cowpox (CPXV) isolates. 25 AKMV genes differed significantly from CPXV-BR at the genomic termini, with 13 unique to one virus and 12 showing truncations or fragmentations between the two [12,13]. AKMV lacked homologs of CPXV013 and CPXV221 while retaining two putative virulence genes absent in CPXV-BR. Six AKMV genes exhibited truncations compared to CPXV-BR homologs, including three predicted to function in virulence [14,15]. AKMV also shared a similar profile with CPXV-BR, covering all families of host range factors. However, differences were observed in 15 factors, including complete absence, indels, low identity, and truncation [16,17].

Public health implications and management of AKMV

The genomic characterization of the AKMV has provided insights into its evolution, transmission, and possible host range. AKMV, which separates from CPXV and all known OPXVs, is the oldest known old world OPXV [17]. OPXV infections in humans are found globally, with viral species spread across Europe and West Asia (CPXV), central and western Africa (MPXV), Colombia and Brazil (VACV), India and Bangladesh (Buffalopox virus), and Georgia (AKMV) [18,19]. The genetic characterization of AKMV suggests a long evolutionary history, potentially dating back decades. This analysis also indicates a heightened capacity for adaptation to its host environment. Genetic variation amongst AKMV isolates points to physical barriers—possibly the Likhi Range—as the cause of isolation inside Georgia. The genome sequence of AKMV is comparable to that of CPXVs, indicating that

humans, cows, and possibly rodents are among the virus's possible hosts [1,20].

AKMV's zoonotic nature raises questions about its potential reservoir host and transmission dynamics. Its broad host range, spanning humans to animals, complicates control efforts and poses challenges for containment and eradication strategies. The lack of vaccination against smallpox in younger populations increases susceptibility to AKMV infection, contributing to the global wave of orthopoxvirus outbreaks [21]. Since the AKMV and other orthopoxviruses share several epitopes, infection with any orthopoxvirus representative induces cross-protective immunity against other orthopoxviruses [22]. AKMV incubation lasts between seven and fourteen days. Direct contact with an infected animal or its bodily fluids can transfer the virus from the animal to humans. Youngsters and those who work with animals have the highest incidence of scratches and abrasions on their skin, which may be an indication of future clinical changes [23]. Clinical lesions in humans are big, ulcerative, inflammatory, and edematous lesions in the skin and occasionally the mucosa. A thick, firm, and black crust has formed [24]. There's also pyrexia, tiredness, a sore throat, and overall malaise, along with local lymphadenopathy. Scars may occur from secondary infections of these lesions. The illness can be severe and widespread in individuals with immunodeficiencies, but in immunocompetent patients, it is self-limiting [24]. There is an increased risk and tendency for epidemic outbreaks and mutated viral strain infections, particularly among the immunocompromised, underscoring the need for public health preparedness [25].

Management of AKMV infections is currently multi-pronged, interdisciplinary, and mostly symptomatic (Table 2). Interventions require bronchodilators, antibiotics, and chest physiotherapy for respiratory tract involvement. Additional strategies to improve respiratory function include nebulization, suctioning, and incentive spirometry. Associated complications such as sepsis demand prompt administration of antibiotics, intravenous fluids, supplemental oxygen, and vasopressors. Oral lesions can be managed with oral hygiene and topical analgesics [26]. Antiemetics and antipyretics with external cooling techniques can attenuate gastrointestinal symptoms and hyperpyrexia, respectively. Skin lesions may require wound dressings and topical antibiotics to prevent secondary skin infections. Anti-inflammatory and analgesic drugs can provide symptomatic relief. Ocular infections require a thorough evaluation and use of antibiotics, antivirals, and corticosteroids [26,27].

There is a need to develop potent antiviral treatments for AKMV. While most viral strains in the OPVX genus have yet to have definite antiviral agents, only two medications—tecovirimat and brincidofovir—have been approved by the FDA to treat smallpox. These medications' approval based on animal research highlights the difficulties in creating cures for illnesses without known human cases. Conversely, brincidofovir targets viral DNA polymerase in a variety of DNA virus families, although it is less effective against some orthopoxviruses, with AKMV yet to be confirmed [28]. Although cidofovir topical therapy has demonstrated potential and has been successfully used to treat skin lesions caused by monkeypox, its potential for managing AKMV is yet to be documented and reported [29,30].

Table 1. Genetic variations in akhmeta virus isolates

Isolate ID	Genome length (bp)	GC content (%)	SNPs	Indels
AKMV_AKHM13-85	221,902	66.5	3	1
AKMV_AKHM13-88	221,911	66.5	3	1
AKMV_VANI10	217,740	66.5	2146	156

**GC= Guanine (G) or Cytosine (C)*

SNP = Single Nucleotide Polymorphism

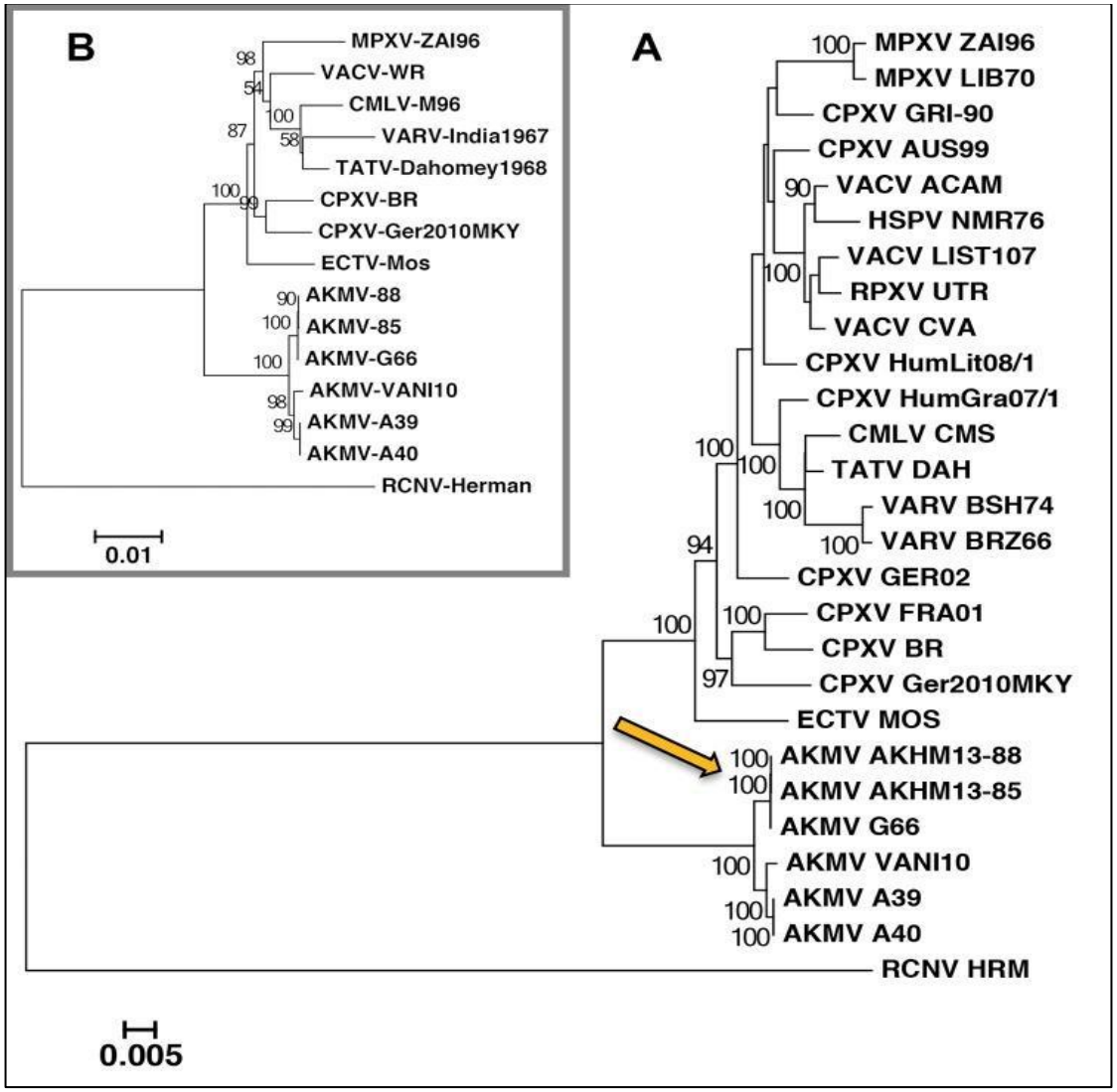
Indels = Insertions or deletions

Table 2. Comparison of clinical management strategies

Management approach	Description	Medications used
Symptomatic treatment	Treat symptoms like fever and pain	Antipyretics, analgesics
Antiviral therapy	Use of antivirals to target the virus	Tecovirimat, brincidofovir
Supportive care	General support including hydration and nutrition	IV fluids, nutritional support

Fig. 1A: Using the raccoonpox virus as the outgroup taxon, a maximum likelihood study of old world orthopoxviruses was conducted. Analysis looked at the connections between isolates of the AKMV and other congeners. (**A)** Nucleotide core tree; the orange arrow points to the evolutionary history at the likely location of the major recombination event that is addressed in the text and marked in orange in

Fig. 1B: Bottom. Less than 80 for the bootstrap value is not displayed. (**B**) The amino acid tree of conserved chordopoxvirus genes replicates the position of AKMVs, which branch off earlier than OPXVs as observed in panel A's nucleotide tree, and displays CPXV-Ger2010MKY in its proper location next to CPX. [2]



Recommendations

Public health preparedness for lethal viruses, such as the AKMV, is imperative; lessons from the COVID-19 pandemic buttress this. The sudden appearance of SARS-CoV-2 emphasizes the necessity of a proactive defense plan to foresee and lessen the effects of new infections. Identifying and destroying viral reservoirs on time is the first preventive measure to stop viral spread to human populations. The significance of metagenomics in viral disease identification and characterization, particularly among closely related animal hosts of similar biological lineages, is crucial. Comprehending the viromics of rodents is essential for conducting efficient surveillance and preventive measures [21]. Mass vaccination is the most effective way to prevent viral disease [31]. A significant portion of the global population is no longer immune to smallpox and other zoonotic orthopoxvirus infections due to the smallpox vaccination program ending after 1980 [32]. This raises the possibility of zoonotic orthopoxvirus spreading among humans, which could alter the ecology and host range of several orthopoxviruses [32]. Additionally, research efforts should focus on advancing the development of newer generations of safe live orthopox vaccines to stop epidemic outbreaks and, thus, lower the likelihood of evolutionary emergence [33,34].

The landscape of bioterrorism preparedness against eradicating pox viruses has significantly changed due to advancements in antiviral research for treating OPXV. Antivirals hold the potential to reduce vaccination risks and provide immune-compromised people with additional protection in the case of a pox breakout. Although there is little data on combination therapy, future studies should expand beyond antiviral monotherapy to personalised combination therapy. In addition, more reliable models to evaluate the effectiveness of antivirals against more virulent strains should be created in light of the possibility of antiviral resistance [35]. Effective treatment of potential AKMV cases necessitates continued research into novel chemotherapeutic drugs with distinct molecular targets, acknowledging that the extensive use of antiviral drugs leads to the emergence of resistant virus strains [36]. The management of AKMV requires epidemiology, community involvement, and surveillance initiatives. Regulations on preventing AKMV disease, such as avoiding contact with reservoir animals and cooking animal products, should be established in affected regions [37,38]. WHO-developed guidelines for safe burial practices and cremation should be followed in line with best infection prevention and control (IPC) practices. Recovering from AKMV should be precautionary, and collaboration between governments and stakeholders is crucial for swift containment [39]. To manage the threat of AKMV and other orthopoxviruses, improving diagnostic capabilities and targeting rapid identification of these viruses are essential. Continuous surveillance and establishing monitoring systems are crucial due to the rise in outbreaks in animals and humans. Adequate supplies of vaccines and therapeutics are crucial for responding promptly and efficiently to outbreaks, facilitating rapid containment, and minimizing the impact of infectious diseases on public health and safety [32,40].

Standardized guidelines for identifying, characterizing, and naming viruses should be used in conjunction with international guidelines set out by appropriate authorized bodies to curb the possibility of stigma [41,42]. The international spread of AKMV emphasizes how closely related public health and national security are, making concerted efforts to combat new viral threats necessary. Mitigating the burden of orthopoxvirus infections such as AKMV requires worldwide collaboration, proactive surveillance, and rapid reaction capabilities. Funding for research, readiness, and reaction is required to protect public and global health [21,43].

Conclusion

In conclusion, this study emphasizes the need for preventative actions to attenuate the threat posed by AKMV and potentially other orthopoxviruses. To effectively respond to evolving biological threats, enhancing diagnostic capabilities, establishing robust surveillance systems, and developing pharmacotherapeutic options, including vaccines, antivirals, and support therapy, is crucial. Furthermore, public health measures, including system preparedness for unforeseen outbreaks, should be prioritized. There is a dire need to align locale guidelines for naming novel infectious diseases with standard international recommendations set by the WHO to prevent possible stigmatization, which may aggravate public health consequences. Concerted international collaborations among relevant stakeholders are imperative to mitigate the risk of localized outbreaks

escalating into global epidemics and to safeguard public health worldwide.

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Competing Interest

The authors declare no conflict of interest.

Author contributions

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Collection and assembly of data: All authors
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All authors have read and approved the final draft and are responsible for the content therein.

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