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Original Research Article

Critical appraisal of Monkeypox (Mpox) in Africa using scoping and systematic review methods

Abdul-Azeez A. Anjorin[1,2,3*#], Ismail A. Odetokun[3,4#], Oluwaseyi S. Ashaka[5], Temitope O. Fadipe[6], Aliyu Muhammad[3,7], Temitope O. Sogbanmu[3,8], Jean B. Nyandwi[9,10], Oyewale M. Morakinyo[3,11], Akeem B. Dauda[3,12], Mutiat A. Adetona[4], Sodiq O. Tijani[13], Wasiu O. Salami[1], Murtala B. Isah[3,14,15], George Gachara[16], Abdulazeez O. Giwa[17], Mohamed Lounis[8,9], Aala M. Maisara[19,20], Ezekiel F. Hallie[21], Ismail O. Adesanya[22], Rasha Mosbah[23,24], Kingsley N. Ukwaja[3,25,26], Mohammed A. Ibrahim[3,27]

Affiliation

[1]Department of Microbiology (Virology research), Lagos State University Ojo, Nigeria.

[2]Africa Centre of Excellence for Innovative and Transformative STEM Education (ACEITSE), Lagos State University, Ojo, Nigeria.

[3]Biological and Health Sciences Working Group, Nigerian Young Academy, Lagos, Nigeria.

[4]Department of Veterinary Public Health and Preventive Medicine, University of Ilorin, Nigeria

[5]Department of Biological Sciences and Biotechnology, Caleb University, Imota, Nigeria.

[6]Department of Biotechnology, Federal Institute of Industrial Research, Oshodi, Nigeria.

[7]Department of Biochemistry, Faculty of Life Sciences, Ahmadu Bello University, Zaria, Nigeria.

[8]Ecotoxicology and Conservation Unit, Department of Zoology, Faculty of Science, University of Lagos, Lagos, Nigeria.

[9]Departmentof Pharmacy, College of Medicine and Health Sciences, University of Rwanda, Kigali, Rwanda.

[10]East African Community Regional Centre of Excellence for Vaccines, Immunization and Health Supply Chain Management, Kigali, Rwanda.

[11]Department of Environmental Health Sciences, University of Ibadan, Ibadan, Nigeria.

[121]Department of Fisheries and Aquaculture, Federal University Dutsin-Ma, Dutsin-Ma, Nigeria.

[13]Department of Medical Microbiology and Parasitology, College of Medicine, University of Lagos, Idi-Araba, Nigeria.

[14]Department of Biochemistry, Umaru Musa Yar'adua University, Katsina, Nigeria.

[15]Biomedical Science Research and Training Centre, Yobe State University, Damaturu, Nigeria.

[16]Departmenof Medical Laboratory Science, Kenyatta University, Nairobi, Kenya.

[17]Departmen of Zoology and Environmental Biology, Lagos State University, Ojo, Nigeria.

[18] Laboratoire d'Exploration et Valorisation des Écosystèmes Steppiques, Faculty of Natural and Life Sciences, University of Djelfa, PO Box 3117, Djelfa 17000, Algeria.

[19] Research Department, Ministry of Health, Khartoum, Sudan.

[20]International University of Africa, Faculty of Medicine, Sudan.

[21] Department of Pharmacology and Toxicology, Monrovia, University of Liberia, Liberia.

[22]US Army Reserve & Hospitalist, Bayou City Physicians, Spring, Texas, United States of America.

[23]Department of Infection prevention and control Zagazig University Hospitals, Sharqia44519, Egypt.

[24] Department of Medical Microbiology, Immunology and Molecular Biology, Military Medical Academy, Cairo, 11774, Egypt.

[26] Department of Medicine, College of Health Sciences, Ebonyi State University, Abakaliki, Nigeria.

[26] Department of Medical Physiology, College of Medicine, David Umahi Federal University of Health Sciences, Uburu, Nigeria.

[27] Department of Biochemistry, Ahmadu Bello University, Zaria, Nigeria.

***For Correspondence: e-mail:** abdul-azeez.anjorin@lasu.edu.ng; **tel:** +234 802 095 6357

[#]Authors [1] and [2] occupy the same position as first authors

Abstract

Africa remains a battlefield for the emergence and re-emergence of deadly aetiologies including the Lassa fever virus from 1969, Monkey pox (mpox) virus from 1970, and Ebola virus from 1976 till date, among others. With the recent index case of mpox following rapid spread from Africa to different continents, a critical appraisal of the disease to x-ray its dynamics in Africa is warranted. This study integrated a mix of scoping and systematic reviews to converse the epidemiology and biosecurity/environmental issues from one health perspective. Our scoping review used major scientific databases based on their relevance and reliability, while the PROSPERO-registered systematic review followed the PRISMA guidelines. Phylogeny analysis was performed to compare recent outbreaks of mpox with the existing genotypic information. The genetic analysis focused on the H3L gene that codes for envelope proteins involved in viral attachment. Transmission of mpox virus was reported mainly in four routes. Animals implicated include monkeys, squirrels, and pigs. Risk factors include age, gender, occupation, climate, travel, political instability, and vaccination status. Different circulating strains were reported with eight-point

mutations found to occur in Africa. Observed clustering within the predominant West African (WA) clade and the recent outbreak strains corroborate the reports of WA clade in other non-African and non-endemic countries. Viral adaptation in the WA clade enhanced person-to-person transmissibility, spreading to over 100 countries. Hence, there is need to address mpox host-associated physiological and biochemical changes, the development of mpox virus-specific diagnostic kits and vaccines, and studies on the disease's socio-ecological, economic and psychological consequences.

Keywords: *Monkey pox virus, Africa, epidemiology, one health.*

1. INTRODUCTION

The emergence of highly virulent aetiologies from Africa knows no boundaries amidst the continent's rising population of 1.4 billion with an annual growth rate of 2.45% (1). To mention a few is the emergence of the Lassa fever virus in 1969 till date, the mpox virus in 1970 till date, the Ebola haemorrhagic fever virus in 1976 till date, and an expected pathogen X virus sooner or later. Just as Coronavirus Disease-2019 (COVID-19) emerged with a resultant total global morbidity of over 755 million, leading to more than 6.8 million deaths as of February 2023, the ongoing multi-country outbreak of mpox that started in May 2022 has resulted in over 85,600 laboratory-confirmed cases as of 7th February 2023, from more than 110 countries where it was hitherto not endemic with over 90 deaths according to WHO (2).

Although mpox virus was first discovered in 1958 in Denmark from a colony of monkeys, it was not reported in humans until 1970 in the Democratic Republic of Congo. It was also reported in Liberia and Sierra Leone in the same year, followed by subsequent isolation in Nigeria and Cote d'Ivoire in 1971. Cameroon reported her first case in 1980 which was later followed by Gabon in 1988. The first human case outside Africa was reported in the USA in 2003 from rodents shipped from Ghana. In the most recent outbreak, the first case report was documented in the United States on 17th May 2022 according to the Centers for Disease Control and Prevention (CDC). On 23rd July 2022, the WHO declared mpox as the 7th aetiology of public health emergency of international concern (PHEIC) WHO (2).

Classically, mpox is a zoonotic disease caused by the mpox virus which belongs to the genus orthopoxvirus and family poxviridae (2-4). Although African rodents are considered the natural reservoir of mpox, the disease was first found among cynomolgus monkeys while infections have been reported in other wild animals like dogs, mice, and squirrels. There are two (2) clades of mpox; the Congo Basin (CB) clade now called clade I and the West African (WA) clade, known as clade II, that are known to cause endemic and sporadic cases in Central and West Africa (Table 1) (4, 5).

Primary transmission of human mpox occurs through exposure to or contact with body fluids of infected animals or handling of infected animals. Secondary transmission occurs through inhalation of respiratory droplets of infected animals directly or indirectly via contaminated fomites, as well as direct contact with infected secretions of patients (4, 6). Human-to-human transmission of the disease is more common among individuals infected with the CB compared to the WA clade (4, 6).

In the past two (2) decades, outbreaks of the CB clade mainly occur in the Democratic Republic

of Congo and the Central African Republic (7, 8). Between 1970 and 2017, Nigeria reported only three (3) confirmed cases of human mpox as a result of the WA clade (4); but from September 2017, the country experienced the largest outbreak with 228 suspected and 60 confirmed cases occurring in about two-thirds of the 36 states in the country (5, 9). After these cases, the virus spread largely across the African continent with more recent cases across the globe (6). For instance, in 2018, a human case of the disease was reported in Western Cameroon where the virus exhibited close genetic relatedness with another mpox virus isolated in Nigeria during the 2017-2018 outbreak (10). Other sporadic cases were reported in Sierra Leone (11) while a total of 76 (3 fatal) cases were reported in Ghana and there is evidence of multi-species involvement from three (3) genera (*Cricetomys*, *Graphiurus*, and *Xerus*) (12). Also, a fatal case of mpox occurring in a wild-living Chimpanzee (Sooty Mangabey) was reported from Côte d'Ivoire in 2012 (13).

Table 1: Reported cases of mpox in humans and animals in Africa (1970–2018)

Country	Year	Location	Number of cases	Number of deaths
Cameroon§	1979	Mfou District	1	0
	1989	Nkoteng	1	0
Central African Republic	1984	Sangha Administrative Region	6	0
	2001	-	4	-
	2010	-	2	0
	2015	Mbomou Prefecture, Bakouma and Bangassou subprefectures	12	3
	2016	Haute-Kotto District, Yalinga	11	1
	2017	Mbaiki Health District	2	0
	2017	Quango Health Districts	6	0
Côte d'Ivoire	1971	Abengourou	1	0
	1981	-	1	-
Democratic Republic of the Congo	1970-2017	Multiple provinces	>1,000/year**	-
Gabon	1987	Region between Lambarene and N'Djole	5	2
Liberia	1970	Grand Gedeh		
	2017	Rivercess and Maryland countries	2	0
Nigeria	1971	Aba State	2	0
	1978	Oyo State	1	0
	2017-2018	Multiple States	89††	6††
Democratic Republic of Congo	2003	Likouala Region	11	1
	2009	Likouala Region	2	0
	2017	Likouala Region	88	6
Sierra Leone	1970	Aguebu	1	0
	2014	Bo	1	1
	2017	Pujehan District	1	0
Sudan	2005	Unity State	19	0

** Democratic Republic of the Congo has reported >1,000 suspected cases each year since 2005.
†† As of February 25, 2018; laboratory-confirmed cases only.
§ Outbreaks have occurred twice (2014 and 2016) in captive chimpanzee groups.
Mpox virus was isolated from a wild caught Sooty Mangabey (*Cercocebus atys*). Source: (14).

Apart from the African cases, the mpox cases occurring mainly due to the WA clade have in the recent past been reported outside of the African continent (15). In 2018, a case was reported in Israel of a man who returned from Nigeria (16) while in 2019, a case was reported about a man who traveled from Nigeria to Singapore (17). In May 2021, a family in the United Kingdom after visiting Nigeria reported three (3) cases of mpox (18). In November 2021, a case occurred in a male patient who traveled from Nigeria to Dallas, Texas (19, 20). As of 7th February 2023, human mpox outbreaks have been reported from over 110 countries mainly in Europe and the Americas with more than 85,000 confirmed cases (2).

With the rapid spread of mpox from Africa to different continents, a critical appraisal of the disease in Africa is required. Unfortunately, such a holistic appraisal of mpox in Africa is not available. Indeed, and by implication, the continual scientific discourse associated with mpox and its negative impacts on the already stretched and overburdened African public health system cannot be overemphasized. In this review, we utilized a mix of scoping and systematic reviews to discuss the epidemiology of mpox in Africa within the context of virology and pathogenesis, clinical features and prognosis, diagnosis, pharmaceutical and non-pharmaceutical options, and biosecurity/environmental issues from the One Health perspective. We adopted both scoping and systematic reviews for each of the methods to complement the limitations of the other to ensure a critical appraisal and a holistic review of the disease in Africa.

2. METHODS

2.1 Literature search for scoping review

For the scoping review, major scientific databases such as PubMed, Medline, Scopus, and Google Scholar were used to gather relevant literature on the epidemiology, biochemistry, treatment, diagnosis, and clinical features of the mpox virus. Some articles were discovered by analyzing citations from other publications. To the best of our knowledge, all the articles from January 1990 to May 2022 that reported mpox virus in Africa were captured in this review article.

2.2 Study design, search strategy and selection criteria for systematic review

Following the best practice for systematic review for health and social care, we submitted and registered our study proposal with the National Institute for Health Research (NIHR) International prospective register of systematic reviews (PROSPERO) with the approval details available at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022337571, and conducted a thorough analysis using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (21). This type of analysis ensures that essential information about the review and its findings is not influenced by the researchers and prevents bias in the article assessment process.

Based on the objectives of this study, we developed six (6) search terms including “mpox prevalence Africa”, “mpox outbreak Africa”, “animal transmission mpox Africa”, “molecular strains mpox Africa”, “origin mutations mpox Africa”, and “One Health control mpox Africa”. These search terms were included in the PubMed, Google Scholar, African Journal Online (AJOL), Ebscohost (Africa-wide info), and Web of Science (WOS) databases. We utilized these databases due to their relevance, reliability, recognition, and robust indexed contents of research articles. Articles included were original articles of various study designs relevant to the search terms and published in English with a clear focus on Africa. Also, articles reporting the prevalence, current cases, and molecular distribution of mpox in Africa were included as well as articles reporting

transmission, biosecurity issues, and One Health control approach of mpox in Africa. Original articles on mpox not reporting on Africa were excluded.

On Google Scholar, only articles on the first ten (10) pages of the search results were considered. The search was conducted in May 2022, hence, articles published after May 2022 were not included in the study. After the initial search, the total results were recorded using the developed search terms. For collaborative screening, all searched articles from the databases saved in CSV files were exported to Rayyan (22).

2.3 Primary and secondary screening for systematic review

During the primary screening of the initial search results, review articles, case reports, and articles whose studies were not based strictly on the search terms and objectives of the study were excluded. Also, duplicate articles (overlapping) from the six (6) databases were removed. The screening process was carried out by four (4) researchers. During a primary screening, studies that did not meet the selection criteria were disqualified based on the details provided in the titles and abstracts while Rayyan web-tool (http://rayyan.qcri.org) was used to validate all the search results in batches.

Unresolved articles/studies during the primary screening were retained for further screening at this stage. In the secondary screening exercise, we considered the full-text papers and included articles relevant to the objective of this systematic review. For efficiency and to minimize errors, the full screening procedure was carried out in batches by paired reviewers. On the accounts of unresolved articles after independent reviews, the reviewers screened the articles together and reached a consensus before a final decision was made on such an article.

2.4 Phylogenetic analysis

Phylogenetic analysis was conducted to compare some recent outbreaks of mpox with the existing genotypic information to suggest the possible source of the outbreak. All nucleotide and amino acid (aa) sequences used in this work were retrieved from the NCBI database of the National Library of Medicine, USA (https://www.ncbi.nlm.nih.gov/). The multiple sequence alignment (MSA) of forty-five (45) selected mpox genomes of African and non-African origins including recent out-break strains and the NCBI reference sequence for mpox virus (NC_003310.1) was performed using MAFFT version 7 (https://mafft.cbrc.jp/alignment/server/) (23) with default parameters. Phylogenetic analyses were conducted using the Maximum Composite Likelihood (24) and Jukes-Cantor (25) methods of the Neighbour-Joining (26), phylogeny algorithm considering 1000 bootstrap replication (27).

Analysis of the *H3L* gene was the primary focus due to its crucial immunological significance because it contains one of the primary epitopes recognized by the host immune system (28). For analysis of the *H3L* gene in selected strains from 1970 - 2022, MSA of nucleotide sequences was performed using two methods. The NCBI-BLAST blastn suite-2 sequences algorithm (29) with NCBI Reference Sequence, NC_003310.1 for mpox virus as a reference and visualized in the NCBI-Multiple Sequence Alignment Viewer 1.22.0. The MAFFT (online service) version 7 (23) with default parameters and the NCBI Reference Sequence, NC_003310.1 for mpox virus as reference and visualization was performed using Jalview version 2.11.2.3 (30).
For analysis of the H3L protein in selected strains from 1970 - 2022, MSA of amino acid sequences was performed using two (2) methods. ClustalW in MEGA 11 (8) with the NCBI Reference

Sequence, NP_536520.1 for mpox virus as reference and AVO21114.1 for buffalopox as out-group. The MAFFT (online service) version 7 (23) with default parameters and the NCBI Reference Sequence, NP_536520.1 for mpox virus as reference and AVO21114.1 for buffalopox as out-group. The visualization was done using Jalview version 2.11.2.3 (30). Phylogenetic trees were constructed using the p-distance (31) and Poisson (32) methods of the Neighbour-Joining (26) phylogeny algorithm considering 1000 bootstrap replication (27). All phylogenetic trees reported in this work were constructed using the MEGA 11 software (33).

3. RESULTS

3.1 Results of scoping review of Mpox (mpox) in Africa

3.1.1 Virology and pathogenesis of Mpox virus in Africa

Mpox virus is a double-stranded DNA virus (130-300 kilobase) and belongs to the genus orthopoxvirus. This same genus is shared by variola (smallpox), cowpox, and vaccinia viruses (34). Viruses in this genus belong to the family poxviridae and sub-family chordopoxvirinae which contains large DNA viruses that synthesize both RNA and DNA in the cell cytoplasm (35). Mpox virus, like other poxviruses has a 200-250 nm brick-shaped coat characterized by surface tubules and a characteristic pleomorphic core that spans between 140-160 nm in diameter. The genome of this enveloped virus is approximately 190 kb with highly conserved regions of about 56-120kb that code for the replication and assembly of viral machinery. This region is flanked by variable regions and terminal repeats which contain four (4) additional open reading frames that are involved in immunomodulation, host range determination, and pathogenesis (34, 36).

Two (2) distinct clades of the mpox virus have been described with known differences in their genetics, clinical manifestation, and epidemiology. These clades are the West African mpox virus, which is predicted to have 171 functional unique genes, 26 non-functional open reading frames (ORF) regions, and vestiges of 10 truncated ORF; and the Congo Basin virus which contains 173 unique genes and 16 truncated ORFs (37, 38). Although both viruses share 170 unique common ancestral genes that are about 99.4% identical at the protein level, the insertion and deletion, as well as substitution in the virulent genes of these viruses, account for their differences (38).

Comparative analysis of mpox with variola virus revealed considerable differences in the regions encoding virulence and host-range factors. An important gene among the virulent genes is a homolog of the vaccinia virus complement control protein present in the Congo Basin clade and absent in the West African clade which may contribute to the reduced virulence of the latter. This protein, although truncated when compared to its vaccinia homolog, is known to retain its complement inhibitory function. The biological activity of this protein is said to account for the immunomodulatory property initiated by the Congo Basin strain of the virus (38).

At the cellular and molecular levels, replication of poxviruses occurs in the cytoplasm of infected cells via a complex and largely conserved morphogenetic pathway. The mpox virus initiates entry into the cell through two distinct viral particles that differ based on their surface glycoproteins (11-13). These wrappings generate either an intracellular mature virus or an extracellular enveloped virus which gives rise to multiple viral ligands that associate with different cell surface receptors as observed with the vaccinia virus. The subsequent processes that lead to cell entry are associated with either viral fusion events at a neutral pH or endosomal uptake that involve actin filaments and low pH-dependent processes (34, 35, 39). The process of viral entry is thought to involve several signaling events in host protein kinase cascades which coincide with the release of viral proteins

and enzymatic factors that disrupt cellular defense mechanisms like the toll-like receptor signaling intended to activate antiviral defense pathways (40). The virus-packaged RNA polymerase, as well as transcription factors, begins the first early gene expression to synthesize viral mRNA. The synthesis of early proteins promotes further uncoating, DNA replication, and production of transcription factors. This is followed by the transcription and translation of intermediate genes to induce the expression of structural proteins, enzymes, and early transcription factors packaged into nascent virions for a new infectious cycle (34).

3.1.2 Biochemical and pathophysiological bases of pathogenesis of mpox disease

Understanding virus behaviour vis-a-vis the virus-host interactions is key to deciphering the druggable targets and making scientific decisions on potential markers required for diagnosis. This is why the understanding of viral pathogenesis at cellular and molecular levels cannot be overemphasized. These physiological changes observed during the infection process cannot happen without some underlying biochemical events surrounding the mpox viral pathogenesis/pathophysiology. The concept of three (3) levels of poxvirus tropism had since been reported to be espoused with cellular tropism. The first is the permissive, semi-permissive, or abortive nature of virus replication in cultured cells of different lineages, after which there are increased levels of virus replication influenced by factors that mediate cellular tropism and tissue-specific antiviral responses, and the third level is influenced by the first two (2) levels of tropism coupled with the overall host immune and inflammatory responses (40). These levels of tropism were supported by poxviruses' ability to bind and permeate both permissive and restrictive cells, but downstream molecular events are aborted specifically in restrictive cells.

It is now clear that orthopox virus assembly comprises the accretion and shedding of several lipid bilayers within the biological membrane, leading to the formation of four distinct forms of virions (41): intracellular mature virus (IMV), intracellular enveloped virus (IEV), cell-associated enveloped virus (CEV), and extracellular enveloped virus (EEV). It is worthy of note that each of these harbors' unique infectivity, immune evasion, and weaponization attributes (42).

Fully permissive viral replication is characterized by three waves of viral mRNA and protein synthesis (described as early, intermediate, and late), which are followed by the morphogenesis of infectious particles. IMV is transported via microtubules and wrapped with a Golgi-derived membrane to form IEV. The IEV fuses to the cell surface membrane to form CEV, which is either extruded away from the cell by actin-tail polymerization or is released to form free EEV. EEV might also form by direct budding of IMV thereby circumventing the IEV form. Non-permissive poxvirus infections generally abort at a point downstream of the binding/fusion step (40). These could demonstrate that there are unique features in specific cell types and point in cell metabolism that contributes to the pathogenesis and viral interactions in the host.

Comparative proteomics of human mpox, based on liquid chromatography-mass spectrophotometry (LCMS) analysis exposed the functions of ORFs 002, 003, 010, and 165(42) which were found to have putative immunosuppressive (ORF 002), structural (ORFs 003 and 010), and unknown (ORF 165) based on their homology to other proteins. ORF 002 encodes a homolog of a secreted tumor necrosis factor receptor from the cowpox virus (43). ORFs 003 and 010 encode proteins that contain ankyrin-like regions (44), and ankyrin repeats are known to form protein-binding domains in a wide variety of proteins (45).

The understanding of the biochemical basis of mpox virus infections while underpinning its pathogenicity in different experimental models suggests that in the event of the mpox virus infection in a cell, two (2) major biochemical events are affected namely, immunoregulation and cell growth. For instance, evasion of the host innate immune system can be linked to the vaccinia virus (VACV) E3 protein homologue present in the mpox virus and has been demonstrated to exhibit full interferon resistance *in vitro*. Moreover, the role of complement control protein in mpox pathogenicity has been reported (46). This modulatory protein suppresses the initiation of both the classical and alternative signaling pathways of complement activation (46).

It was evident that this viral biomolecule is an important immunomodulatory protein in mpox pathogenesis even though it cannot independently explain the increased virulence observed within the Congo Basin clade of mpox virus (46). It is also an established fact that natural killer cells have a role in bridging innate immunity and adaptive immune responses against viral infection. Interestingly, the mpox virus has been found to induce massive expansion of natural killer cells without any measurable natural killer cell functions by the host (47), which is yet to be fully understood.

In another study, cytokine profiling of serum from acutely ill humans collected during mpox active disease surveillance (2005–2007) in the Democratic Republic of the Congo revealed elevated cytokine concentrations in all samples with marked overproduction of interleukin [IL]-2R, IL-10, and granulocyte macrophage-colony stimulating factor observed in patients with serious disease (48).

The idea that severe human mpox disease could be complicated by bacterial sepsis has been presented. Experimental infection of mpox virus in a cynomolgus monkey gave rise to a fulminant and characteristic flat red rash similar to the haemorrhagic type of variola major (smallpox) that results in widespread haemorrhage in the skin and mucous membranes, where the pustules remain flat which is usually fatal. It was, therefore, suggested that bacterial sepsis could upturn events that could lead to neutropenia and excessive inflammatory cytokine responses with neutrophils upsurge which play key roles in the pathogenesis of systemic and fulminant human mpox virus infections (49).

3.1.3 Clinical features and prognosis of human mpox disease in Africa

A range of conditions can give rise to skin rashes which could be challenging to differentiate solely on the basis of clinical presentation. The clinical presentation of human mpox in Africa includes a prodrome of fever, headache, night sweats, myalgia, and coryzal illness. Patients also develop significant peripheral lymphadenopathy which is a key differentiating feature of mpox from smallpox (50). After 1 to 2 days, lesions may occur in the mucosal surfaces and skin, particularly in the face, scalp, trunk, and limbs, (including palms and soles), and are centrifugally concentrated (40, 44, 49, 50).

The rash may or may not involve the whole body, and it may vary from a few scanty to more widespread lesions. In unmanaged cases, within 2-4 weeks, the lesions evolve from macular phase to papular, vesicular, and subsequently pustular phases. The progression of the rash from raised lesions to the development of pustule lesions is accompanied by fever, chills, enlarged lymph nodes, headaches, and muscle aches, which normally disappear within 2-3 weeks are some of the fundamental and visible symptoms earlier reported among humans (51). The pustular lesions are

firm, deep-seated, and 2 to 10 mm in size (40, 44, 49, 50). After 5 to 7 days of having pustular lesions, crusts begin to form and subsequently desquamates over one to two weeks, and the condition resolves around three to four weeks after the onset of symptoms. After all the crusts have fallen off, the individual is considered to no longer be infectious (49, 50).

Generally, the prognosis of human mpox cases in Africa is remarkable as the majority of affected persons have mild disease and tend to recover within weeks. Mortality can occur but it varies depending on the clade and it is generally higher in children, young adults, and immunocompromised individuals. Although there are no specific treatments for mpox, the smallpox vaccine has demonstrated about 85% effectiveness in the prevention of the development of human mpox outbreaks (35).

3.1.4 Laboratory diagnosis of mpox virus

In the areas of establishing reliable and widely acceptable methods of mpox epidemiological surveillance and disease diagnosis, scientists had successfully put forward arrays of molecular biology-based approaches for early detection of the disease. For instance, the routine detection of mpox DNA from clinical and veterinary specimens, vis-à-vis infected cell cultures can be achieved by real-time or conventional polymerase chain reaction (PCR) systems designed based on conserved regions such as the extracellular-envelope protein gene (*B6R*), DNA polymerase gene (*E9L*), the subunit 18, *rpo18* of DNA dependent RNA polymerase and *F3L* gene (50). It has been suggested that two conserved viral gene targets that are combined could provide a reliable and sensitive diagnosis and other nucleic acid testing platforms have been developed with this advantage. Limited viraemia of mpox has made PCR blood tests non-diagnostic, however, swabs, scabs, and fluid from aspirated lesions are diagnostic because of the stability of the virus in these samples. In addition to PCR, restriction length fragment polymorphism of PCR-amplified genes or gene fragments has been developed to distinguish variola, vaccinia, cowpox, mpox, camelpox, ectromelia, and taterapox viruses (52).

Antigen or antibody detection from plasma or serum is not specific for diagnosis because of serologic cross-reactivity between orthopox viruses and false positive results from previously or recently vaccinated individuals against smallpox. However, the detection of IgG and IgM antibodies in acutely ill individuals collected 21 days apart, especially in the first week of illness can aid in diagnosis. Researchers have identified 69-126-3-7 antibodies that bind specifically to the A27 protein of human mpox and there is hope for its diagnostic and epidemiological utility. Culture-based testing and electron microscopy for mpox is not performed routinely in clinical or diagnostic facilities due to the high technical skill and facilities required. The merits and demerits of the possible diagnostic techniques for human mpox disease (Table 2).

Table 2: Merit and demerits of mpox diagnostic techniques

Method	African Countries	Usage	Sample Type	Merits	Demerits	Notes	Ref
PCR	Nigeria, South Africa, Egypt, Cameroon, Morocco and Ghana	Frequently used	Skin lesion/exudate	Highly sensitive and specific	Quite expensive	Highly recommended and mostly used	(53)
			Oropharyngeal swab	Requires less time for detection	Does not determine infectivity		
Electron Microscopy	Nigeria, South Africa, Egypt and Ghana	Not Frequently used	Swab of lesion surface	Does not require organism-specific reagents	Requires high technical skills and facility		(54)
Viral Culture	Nigeria, South Africa, Egypt, Cameroon, Morocco, Sudan, Democratic Republic of the Congo and Ghana	Not Frequently used	Swab of lesion surface	Determines infectivity	Requires appropriate experience and containment facilities	Not routinely used	(53)
Serology	Nigeria, South Africa, Egypt, Cameroon, Morocco, Sudan, Democratic Republic of Congo, Benin and Central African Republic	Frequently used	Serum Plasma	Easy to use	Prone to contamination, Insufficient level of sensitivity	Not routinely used	(54)
ELISA	Nigeria, South Africa, Egypt, Cameroon, Morocco, Sudan, Democratic Republic of Congo, Benin, Central African Republic and Benin,	Frequently used	Serum Plasma	Time saving High efficiency High specificity	Tedious assay procedure, Insufficient level of sensitivity, Prone to contamination	Routinely used	(54)
Fluorescence Immuno Assay	Nigeria, South Africa, Egypt and Ghana	Not Frequently used	Serum Plasma	Rapid Easy to use Reliable	Low level of sensitivity Prone to contamination	Not routinely used	(54)
Rapid Detection techniques (RDT)	Nigeria, South Africa, Egypt, Cameroon, Morocco, Sudan, Democratic Republic of Congo, Benin, Central African Republic and Benin,	Frequently used	Swab of lesion surface	Rapid Easy to operate	Low level of sensitivity and specificity, Prone to contamination	Not routinely used	(54)

3.1.5 Pharmaceutical and non-pharmaceutical options to manage mpox disease

It is believed that mpox is self-limiting and infected patients can recover without treatment.

However, prophylactic interventions such as the vaccinia vaccine (smallpox vaccine), vaccinia immunoglobulin (VIG), and antiviral medicines can be used to control an outbreak and prevent the disease from spreading (55). It has been reported that smallpox vaccine can be up to 85% effective in preventing infection with the mpox virus when given before exposure to the virus (56). The effectiveness of smallpox vaccines against mpox virus is well explained by the existing similarities between the two viruses, and the potential cross-protection provides evidence that smallpox vaccines can be used for mpox (8).

Three (3) smallpox vaccines that are being considered for the prevention of mpox in Africa include ACAM2000®, Aventis Pasteur Smallpox Vaccine (APSV), and MVA-BN (Imvamune, Imvanex or Jynneos) vaccines. ACAM2000® is the oldest smallpox vaccine which contains the live vaccinia virus. It was licensed by the U.S. Food and Drug Administration (FDA) in 2007 for active immunization against smallpox disease in persons with a high risk for smallpox infection (57). ACAM2000® vaccine was previously proven to protect against mpox in cynomolgus macaques and dogs (58, 59).

The other live vaccinia virus is the APSV. Although it is not formally approved, its potency and efficacy profiles were shown to be similar to those of ACAM2000® and can be used if other vaccines run out (57). The newest and only approved vaccine specifically for preventing mpox infection is MVA-BN. It is a live but modified form of the vaccinia virus called vaccinia Ankara which consists of a two-dose vaccine. The MVA-BN vaccine was proven effective and safe by a wide range of animal and clinical studies (19, 60-62)

Apart from vaccines, some of the existing antiviral medicines used to treat orthopox virus infection may be used alone or in combination with vaccines to treat mpox. https://www.sps.nhs.uk/medicines/tecovirimat/. Tecovirimat interferes with a protein found on the surface of orthopox viruses to counteract their infection and brincidofovir (Tembexa) inhibits viral replication through selective inhibition of orthopox virus DNA polymerase-mediated viral DNA synthesis. Both medicines reduced viral titers in patients infected with mpox viruses in the United Kingdom (62). Similarly, higher doses of cidofovir, an active form of brincidofovir, showed promising results in reducing mpox lesions in monkeys (63). In addition, the combination of ACAM2000® and tecovirimat resulted in reduced mpox virus-associated lesions in non-human primates (64). Post-exposure administration of ACAM2000® alone did not prevent severe mpox disease or mortality while post-exposure treatment with tecovirimat alone or in combination with ACAM2000® conferred full protection. Moreover, tecovirimat treatment delayed until day 4, 5, or 6 post-infection was 83% (days 4 and 5) or 50% (day 6) effective (65).

On the other hand, it is advised to protect from mpox infection through the proper use of personal protective equipment such as wearing masks, googles, gloves or specific impervious long-sleeved gown especially in clinical settings treating mpox-infected patients. Additionally, the protection of compromised skin and mucous membranes, rehydration therapy and nutritional support as well as supportive treatments to minimize or reduce common symptoms such as fever, headache, pain and others must be provided as part of the management therapy for mpox.

3.1.6 Biosecurity/environmental issues associated with Mpox virus

Biosecurity may be referred to as processes, methods, procedures, interventions, policies and/or frameworks which are put in place to exclude, eradicate, effectively manage or mitigate the risks

posed by intentional or accidental release or occurrence of harmful pests, invasive alien species, disease agents of all microbial entities (including viruses, bacteria, fungi, amongst others), plant, animal or human origin capable of transmission to humans, animals, plants with adverse public health outcomes (33, 66, 67). Biosecurity is now of tremendous importance and has received attention from scientists, policymakers, industry practitioners and other stakeholders especially after the onset of the COVID-19 pandemic. Anthropogenic climate change attributed to increased human activities has resulted in increased emission of greenhouse gases thereby causing global warming at an unprecedented pace (68). The impacts of climate change on other indices such as increasing global average surface temperatures, increased precipitation with sea level rise, among others have resulted in shifts in the tolerance range of pests and disease vectors, increased extreme weather events (excessive heat and rainfalls), changes in biodiversity due to potential shifts in the ranges of invasive alien species, disease vectors, and food security (69). This may also be linked to the outbreaks of mpox virus in countries that were hitherto non-endemic for the disease which caused negative impacts on health, economy, social and environmental components. In fact, a vital aspect of consideration in disease transmission and circulating clades is the potential influence of environmental variables/climate variables. Mpox being a zoonotic disease like the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) raises concern about the relationships between the etiology and known or unknown animal hosts to human transmission pathways. Anthropogenic environmental drivers like land use changes particularly deforestation, expansion of agricultural lands, intensive livestock, and wildlife farming as well as trade pose pandemic risks from viruses and other pathogens of zoonotic origin (67, 70, 71) (Figure 1).

According to Mills *et al* (69), climate change may influence the frequency and distribution of vector or non-vector-borne zoonotic diseases through any or all of the following four (4) mechanisms; “a) changes in the population density of the host or vector that results in increased contact with humans or other hosts and vectors; b) range shifts in the host or vector distribution that bring these hosts and vectors into contact with new human populations; c) changes in the prevalence of infection in the host or vector population that would increase the frequency of human (or other host or vector) contact with an infected host or vector; and d) changes in pathogen load brought about by changes in rates of reproduction, replication, or development in the hosts or vectors that affects the likelihood that a human (or other host or vector) contact would result in pathogen transmission.”

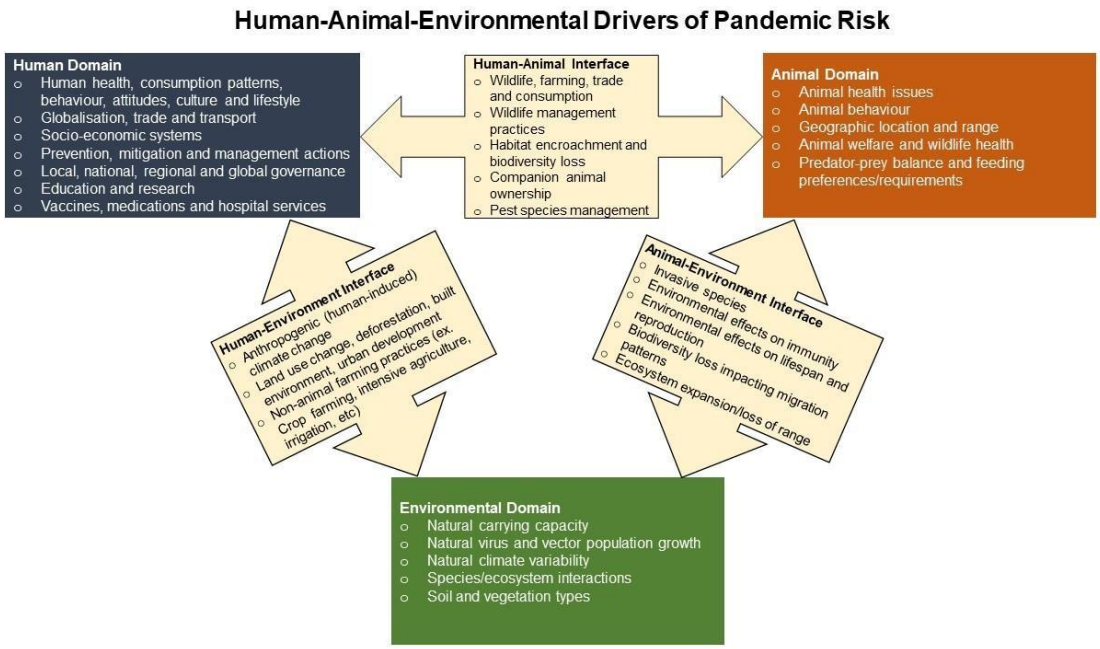

Figure 1: Human-animal-environmental drivers of pandemic risk modified from Mandja (72).

3.2 Results of the systematic review of mpox in Africa

3.2.1 Distribution of articles included in the systematic review

A total of 58 articles were included in this review (Figure 2). The articles comprise records obtained from at least 13 countries in Africa (Supplementary Table 1). These records include published studies from 1972 to 2021. Most of the studies were carried out in the central part of Africa, especially the Democratic Republic of Congo (7, 8, 53, 73-82) and Zaire (83, 84).

Furthermore, many of these studies reported the occurrence/outbreaks, diagnoses, and isolation of mpox (Supplementary Table 1). The case occurrence reported varied from 5 to 1057 confirmed cases both in humans and animals. These cases were confirmed from different sample types such as scabs (7, 8, 83) blood/sera (7, 8, 73, 74, 79, 83, 85-87), organs (4) vesicles (7), pustular fluids (53, 83), skin lesions and crust samples (7, 30, 46, 79, 81, 85) using various detection and isolation methods. Blood/sera and vesicles from suspected/ infected humans or animals were mostly used to diagnose mpox in Africa. The diagnosis of mpox infection in Africa before 2007 was largely through the use of haemagglutination inhibition (4, 7, 73, 83) fluorescence antibody technique (83), electron microscopy (83), radioimmuneoabsorption (83), viral isolation (83) and serology (7, 83). However, in the last decade, molecular-based methods such as conventional PCR (7, 79, 81, 85) real-time (74, 78, 79) and genome sequencing (77) were utilised.

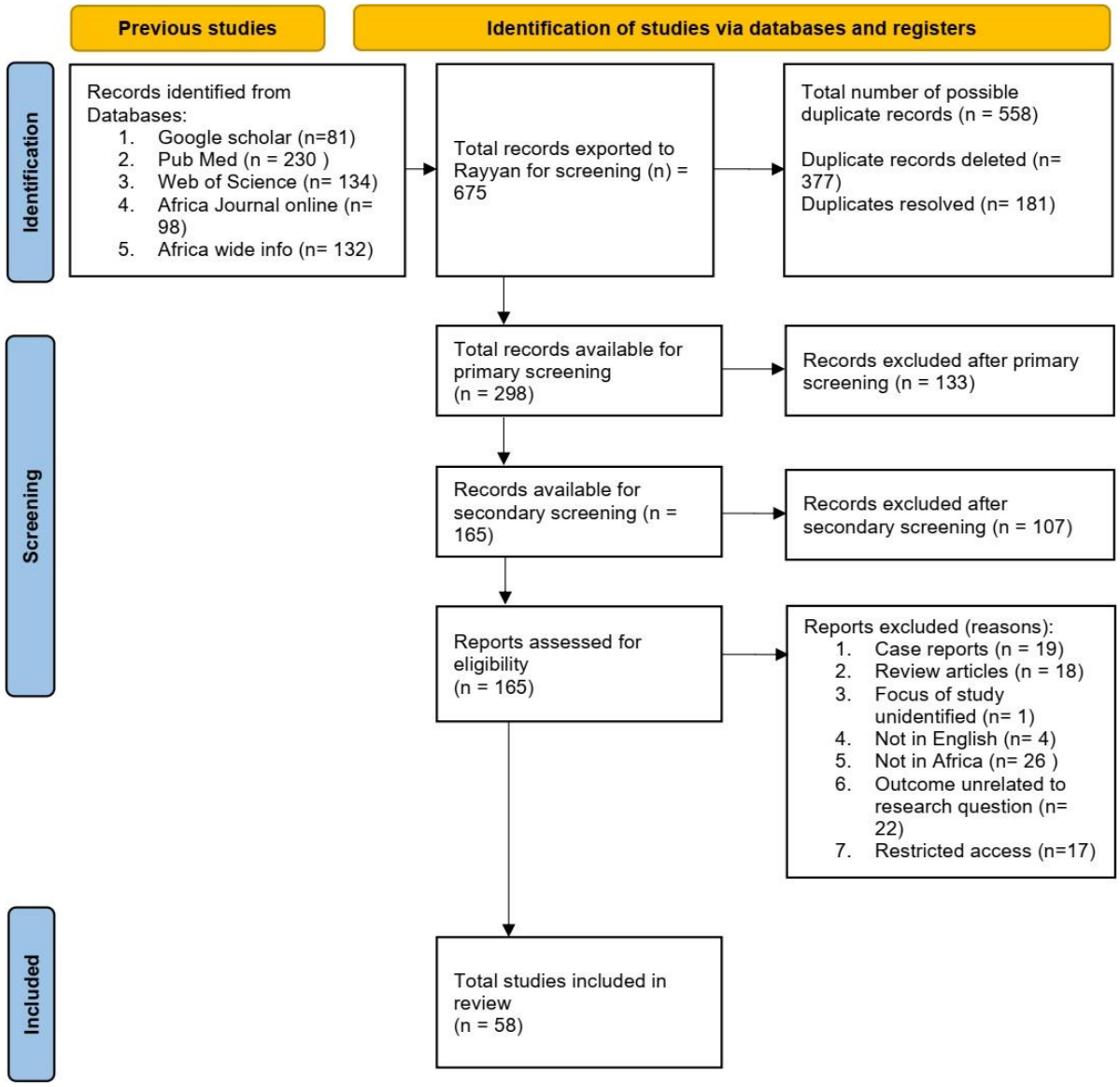

Figure 2: PRISMA flow diagram for articles on Mpox (mpox) in Africa from searches of databases and registers.

3.2.2 Sources, transmission modes, and risk factors to Mpox in Africa

Most studies reported humans and animals as the host in mpox infection and outbreaks, though various animal species were believed to be the sources of mpox infections (Supplementary Table 2). The animals reported include monkeys (83), the Gambian pouched rats (73, 83) squirrels (94), elephant shrews (73), gazelle (73), and pigs (73). Reported circulating strains of mpox on the African continent include Congo-8, Liberia-1, Liberia-2, Sierra Leone (V-70 1 266) (75), MPV-ZAI (76), MPV ZAI-96-I-16 (76), Central African clade (7, 37, 78, 86, 88), West African clade (15, 37, 53, 77, 88) and the Congo basin mpox virus (85) identified with novel genomic structural variation related to the Congo Basin mpox virus clade in humans. The West African clade is the most documented strain circulating on the African continent. Transmission of mpox infection has been reported to occur in mainly (4) ways spanning the human-animal-environment interface, and human-human (4, 7, 15, 77, 78, 83, 85, 86, 79, 80, 89) zoonotic (4, 77, 79-81, 83, 89), cross-species (90) and human/animal-environment (7, 79, 83).

Reported risk factors for mpox infection in Africa include age (79, 80, 83-85, 89), sex (79, 80, 89), occupation (73, 79-81, 89), climate (91), contact with infected animals/humans, habitat/vegetation (7, 73, 74, 78, 81, 83, 85, 92), travels (7), health conditions (85, 93), political instability (77) and vaccination status (7, 8, 78, 83, 84, 89).

3.3 Results of the phylogenetic analysis

Phylogenetic analysis of selected forty-five (45) mpox virus genome sequences showed two (2) distinct clades of Central and East African strains (including NC_003310.1) and West African strains. All the twelve (12) recent outbreak strains clustered within the West African clade and specifically in the Nigerian sub-clade (Figure 3).

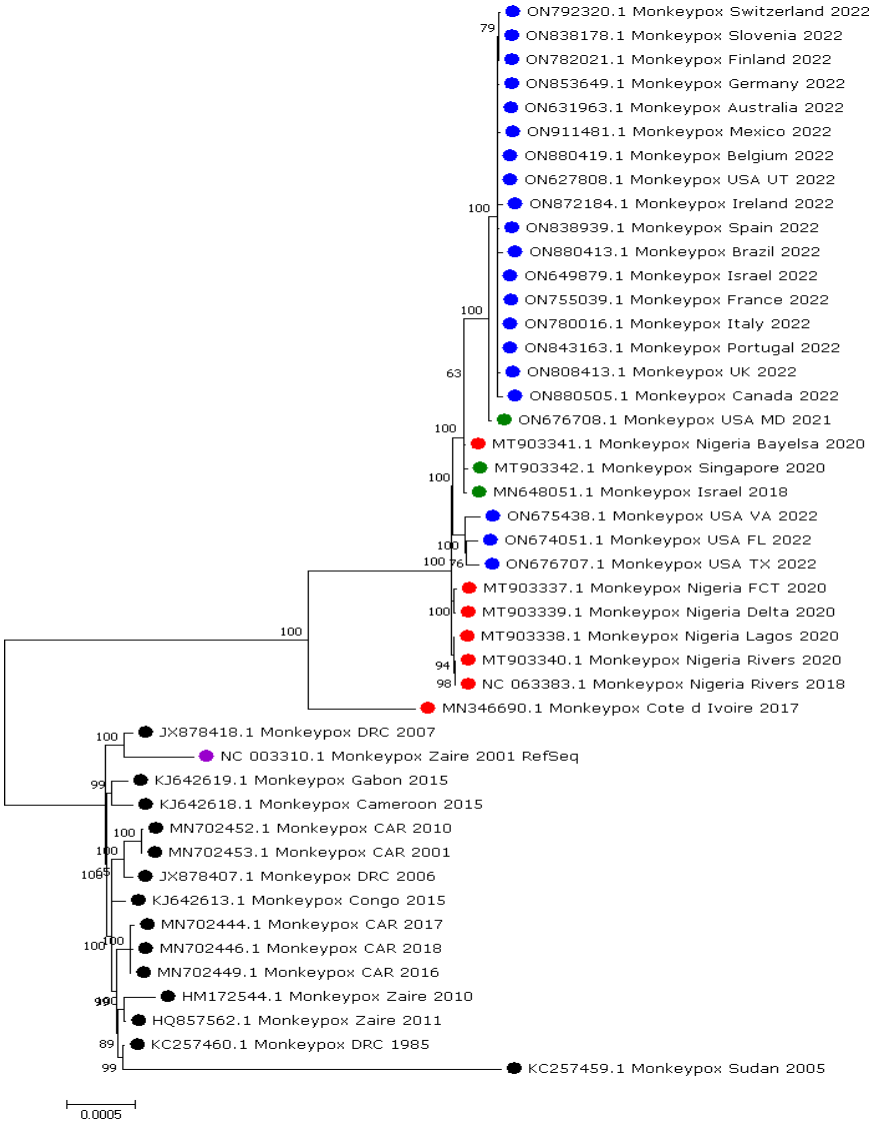

Figure 3: Neighbour-joining phylogenetic tree of mpox viruses. The neighbour joining/maximum composite likelihood tree generated from MAFFT alignment shows the reference genome, NC_003310.1 (purple), Central and East African strains (black) West African strains (red), recent out-break strains (blue), and other non-African strains (green).

The *H3L* gene contains 975 nucleotides translated to 324 amino acids in the reverse direction i.e., translation begins at nucleotide 975. Eight (8) point mutations (substitution) were seen in the

aligned *H3L* gene nucleotide sequences of the twenty (20) selected mpox strains (including the ref seq) (supplementary Table 3).

Of these eight (8) points mutations (substitution), three (3) are missense mutations (e, g, and h) in the second nucleotide of the codon corresponding to their translated amino acid while five (5) are silent mutations (a, b, c, d, and f). The point mutation, A (ref seq NC_003310.1) – G (others) at position 644 results in the 111th translated amino acid changing from isoleucine (ref seq, NP536520.1) to threonine (others). The point mutation, G (ref seq NC_003310.1, DQ011156.1, DQ011157.1, MN346690.1) – A (others) at position 965 results in the 4th translated amino acid changing from alanine (ref seq NP536520.1, AAY97690.1, AAY97491.1, MN346690.1) to valine (others). The point mutation, G (ref seq NC_003310.1 and others) – A (DQ011156.1, DQ011157.1, MN346690.1) at position 971 results in the 2nd translated amino acid changing from alanine (ref seq NP536520.1 and others) to valine (AAY97690.1, AAY97491.1, MN346690.1). Supplementary Figure 1 shows the alignment of H3L protein aa sequences with aa changes associated with the 3 missense mutations.

Phylogenetic analysis of the H3L amino acid sequences shows a high similarity between the strains causing the recent outbreak and the Nigerian strain as observed with the genome-based analysis (Supplementary Figure 2). The three amino acid sequences, AAY97690.1 (USA 2003), AAY97491.1 (Liberia 1970), and MN346690.1 (Cote d'Ivoire 2017) clusters with the reference sequence NP536520.1 (Zaire 2001). This is expected based on the SNPs accounting for the three missense mutations associated with these strains.

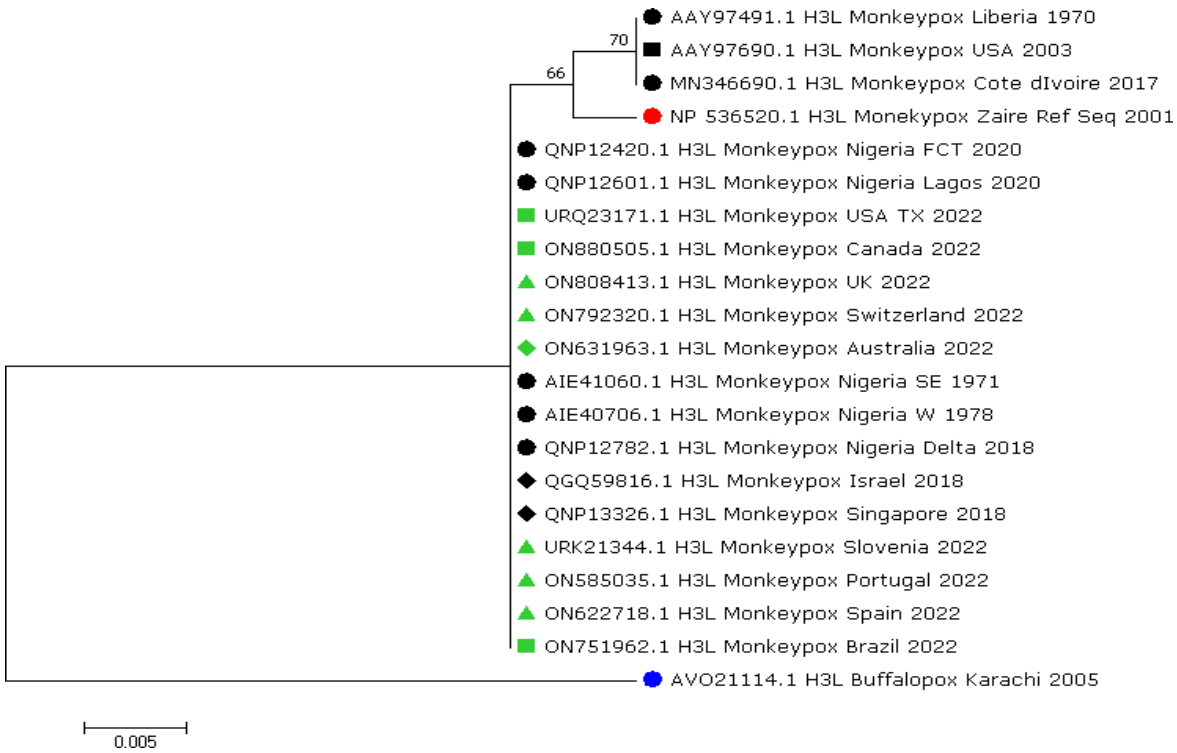

Figure 4: Neighbour-joining phylogenetic tree of H3L amino acid sequences of some mpox viruses. The neighbour joining / p-distance tree generated from ClustalW alignment shows the reference sequence, NP536520.1 (red), West African strains (black circle), US strain (black square), Israel and Singapore strains (black rhombus), Recent out-break strains (green) and out-group (blue).

4. DISCUSSION

The first emergence of mpox virus to the scientific community was from outbreaks in non-human primates whereas the detection of the first human case was about a decade later (61, 75, 94, 95). In the course of a few decades before the late 1970s, this zoonotic disease has spilled over sporadically into the human population even during the smallpox eradication program. In 1986, it was admitted that there was a confusion of mpox with smallpox during post-eradication surveillance (83). The mpox outbreaks experienced at this time were concluded to be zoonotic and that person-to-person transmission of this virus is rather difficult (83). This is a pointer that at the time of the spillover of infections from animals to humans, the mpox virus was not well adapted for effective transmission from person to person.

Another critical factor in the explanation of the evolution of mpox is the smallpox vaccination. Smallpox was declared eradicated in 1980 with aggressive vaccination campaigns by the WHO (96). At this time, the vaccinia vaccine was said to have coincidental immunity against smallpox which could have underpinned the emergence of the mpox virus on an epidemic scale (96). In 1988, a more common outbreak of mpox due to declining smallpox immunity was predicted, which is obviously correct from today's narrative (96). The epidemiological work of Feng *et al.* (97) in which they detected low-level binding antibodies against mpox proteins among persons born in and after 1980 than those born in the pre-smallpox vaccination era, further gives support to the assertion.

Viral fitness and adaptation could contribute to the human-to-human transmission of mpox virus. In 2003, in the Democratic Republic of Congo, seven (7) cycles of uninterrupted mpox transmission were observed (98). As discussed previously, the waning herd immunity could contribute to this occurrence among humans. In Africa, the introduction of mpox to humans from an unidentified animal reservoir in West and central Africa resulted in sporadic introduction into the human population. Poxviruses are unique in that they have a specific host range (99). One major evolutionary driving force of these viruses is co-speciation. For example, in the case of mpox virus, which has a zoonotic ancestry, the virus is shaped in other hosts by the constraints of the ecological niche which makes it stable in its new host (99, 100). The orthopoxvirus genus infects a wide range of mammalian species, including humans (101, 102). Despite this fact, the presence of gene-specific determinants responsible for the diverse host-range phenotypes guarantees infection in some hosts (101). This supports the hypothesis that the interactions of the mpox virus with other hosts including humans different from its natural reservoir could have been responsible for the host variability as observed in the various interactions with other non-human host species. This could have resulted in three (3) possibilities which include: single base changes causing amino acid variation or variation in regulatory regions; acquisition of new genetic information; and the gradual loss of genetic information and coding genes through progressive deletion of DNA sequence (99). In the case of mpox virus, the presence of non-synonymous mutations in the coding regions of host recognition elements could have contributed to viral fitness (103). When the West African and Congo basin clades are being considered, there is evidence of substitutions, insertions, and deletions as documented by (38) which is said to have an influence on the virulence of the Congo basin clade over the West-African clade. It is a possibility that in the future more virulent forms of this virus may emerge close to what was seen with variola major.

Before 2007, the mainstay of laboratory diagnosis for mpox disease was using serological techniques such as haemagglutination inhibition, fluorescent antibody technique,

radioimmunoabsorption, and western blot. All these techniques are antibody-based and were used for the epidemiological characterization of outbreaks, compared to the broad applications of the current molecular techniques. Limitations of serological techniques such as serological cross-reactivity with orthopox viruses (104), waning of antibody response in relation to the time of infection and vaccination status, inconclusive results and the challenges of obtaining convalescent samples, may have impact on the results obtained (105). Although, the probability of a miss out is rare in an epidemic situation, the clinical characteristics of mpox has been said to differ among those vaccinated against smallpox and those that are unvaccinated which could have impacted on the type of lesions and severity of illness associated with this virus (83, 106).

It can be said that viral adaptation in the 2022 outbreak of mpox has given rise to a pathogen that is a public health emergency of international concern. In this study, the observed clustering within the West African (WA) clade (Nigerian sub-clade) of the mpox virus in the twelve (12) recent outbreak strains corroborates the reports of the WA clade in other non-African and non-endemic countries in recent pasts (16-19). This clade has been reported to result in the largest outbreak of the WA clade in Nigeria occurring in 2017 with most of the cases emanating from Bayelsa state, in the Nigeria-Delta region of Nigeria (9). It can be said that the viral adaptation in the West African clade, which can be represented in the various mutations in regions predicted for host recognition is a source of fitness-enhanced person-to-person transmissibility that has culminated into its spread to over 110 countries in the world as of 7th February 2023.

The genetic analysis conducted here focused on the *H3L* gene that codes for the viral envelope protein involved in the attachment to human target cells and the internalization of the virus which is also critical in epitope recognition for the host immune system (103). Eight (8) point mutations were observed to occur in Africa which resulted in different types of mutations (missense, silent, and point mutations) depending on the location of occurrence. The significant mutations led to amino acid changes from isoleucine to threonine at position 644 and alanine to valine at positions 965 and 971. This is consistent with the variability of 21 amino acids out of 324 amino acids (6.5% of the complete protein sequence) when compared to the H3L protein of the variola virus (103). We believe that these mutations contribute with other epidemiological factors to its dispersal into other geographic locations and potentially adapt to new hosts across new regions. Molteni and Forni (107) also alluded to this fact and suggested that mpox could have evolved as a result of immune selection of the *H3L* gene which encodes an immunodominant protein that is a major target of neutralizing antibodies.

Mpox, as a zoonotic disease, requires prevention and control strategies that need to look beyond human beings but also every other organism along the chain of transmission. Among the animals implicated in the outbreak of mpox are non-human primates (including, monkeys, chimpanzees, and Gorilla) (11, 92, 108) and rodents (including, African dormice, squirrel, and giant pouched rats) (12, 109). So, an approach that will have a wide view into the management of humans and non-humans involved in harboring and transmitting of the virus may be rather more effective, hence, the consideration of the One Health approach. Currently, there is no universally agreed definition of One health. However, attempts have been made including that of the One Health Commission, which defined it as "the collaborative effort of multiple disciplines to obtain optimal health for people, animals, and our environment". Also, One Health initiative task force (OHITF) defined it as "the promotion, improvement, and defense for the health and well-being of all species by enhancing cooperation and collaboration between physicians, veterinarians, and other scientific

health professionals and by promoting strengths in leadership and management to achieve these goals" (110). In line with One Health, the factors that can be of great importance to the management of outbreaks and control of mpox disease are vaccination, improved surveillance, native and non-native/wildlife-human interactions management, and understanding of the ecological status (12). Vaccination with the smallpox vaccine, which has been reported to be over 85% potent to prevent mpox disease (56) can be an option in an epidemic situation. In addition to that, surveillance is highly essential for early detection and raising alerts for necessary responses. Animal/wildlife-human interactions must be continuously interrogated for a proper understanding of the means and mode of transmission. It is important to note here that the reservoir host of the mpox virus is still an issue of debate. However, Doty *et al.* (74) suggested that rodents are the primary reservoirs and a later revelation by the CDC (111), suggested that the natural reservoirs are not known yet. Much research has implicated ecological status as a factor in the transmission of mpox virus; more cases have been reported in disturbed areas compared to the non-disturbed forest (74, 79). Coordination and effective communication among the actors along the transmission chain are very important to the successful prevention and control of the disease.

Several environmental and biosecurity-related issues may be responsible for this observation. Environmental disturbances such as changes in land use, deforestation, expansion of new human settlements, which may lead to more interactions of human populations with wildlife including known mpox virus animal hosts like monkeys and rodents, and human travels (8) may be responsible for the observed WA clade mpox virus recent multi-countries transmission. The environmental risk factors may be further exacerbated by insecurity issues in Africa, especially in endemic states, limiting surveillance, and other biosecurity efforts to curb the transmission. In recent months, Africa has witnessed an unprecedented exodus of its citizens to other countries of the world for various reasons, especially economic, security and educational reasons. This increased travel, which may be beyond the carrying capacity of the aviation sector, may limit the level of biosecurity measures for outbound and inbound travelers.

Strengths and limitations of the study

One of the main strengths of this study is that the registered systematic review was conducted according to the PRISMA guidelines with multiple databases which covers a large number of published manuscripts and avoids selection biases. Also, it covers all manuscripts related to the epidemiology of mpox including the origin, prevalence/incidence, transmission, diagnosis and control which will help in understanding of all chapters related to this disease. The manuscript is to our knowledge the first review with a one health approach focused on mpox in Africa.

However, some limitations to the accuracy of the results are acknowledged. First, the study included only published manuscripts in English, thus excluding publications written in other languages that could be helpful in understanding the disease. Second, this review included publications with different approaches, type of surveys (prospective/retrospective) with varying durations, type of samples (swabs, and blood), notions (origin, transmission, and control) and techniques (serology, PCR, and cultural isolation), thus increasing the panel of data and making comparisons more complex. Lastly, the review was limited to articles published before May 2022 and consequently eliminated recent published manuscripts in African countries which could be helpful in understanding the disease in Africa and its possible relation with the new epidemic in the non-endemic countries. Our systematic analysis was restricted to published studies cutting across non-interventional studies which could have potentially introduced publication bias.

However, many of the studies identified did not evaluate the effect of an intervention on Mpox which makes publication bias unlikely. An additional limitation is that most papers were screened with their data duly extracted by only two reviewers. All the papers reviewed were with adequate study objectives thereby limiting the risk of bias. There was also no industry influence on the published studies included.

5. CONCLUSION AND FUTURE PERSPECTIVES (Research gaps and policy implementation needs)

Although some efforts have been made toward the understanding and control of mpox virus infection in Africa, our present review has identified a number of research gaps that should be filled to obtain a holistic strategy for addressing the disease.

1. It was fascinating that a lot of research efforts have been made in understanding the molecular biology of the virus, but **the strategies adopted by the virus to alter the host physiology and/or biochemistry are yet to be fully delineated**. Deciphering such vital host-associated physiological and biochemical changes will deepen the current understanding of the clinical manifestations of the disease. Obviously, this could open novel avenues for treating the disease. In fact, this knowledge gap could be the basis for the unimpressive number of drug discovery trials and efforts targeting the disease. Meanwhile, this is an important aspect to be considered with utmost attention since the African continent relies mostly on drugs and other chemotherapeutic agents in managing the myriads of diseases affecting it. Hence, **there is a need to promote African-led drug discovery campaigns against the mpox virus**.

2. Diagnosis is one of the key variables that determine the success of control options for a number of diseases. It was thus surprising to note, from the present review, **that there is no mpox virus-specific rapid diagnostic kit**. The available rapid diagnostic tests for the virus are largely designed for other viruses such as smallpox or other orthopox virus and were simply adapted to the mpox virus through re-purposing or repositioning approaches. Meanwhile, this should not be tenable because of species-specific factors and especially for a disease like mpox virus infection that sporadically ravages the African continent. In fact, the same observations and arguments could be extended to the other diagnostic methods which call for concerted efforts to produce highly specific and sensitive diagnostic tools for the disease.

3. Also, it is worrisome from the present review, that **there is no specific vaccine for mpox virus** as the present vaccines are originally made for smallpox or other orthopox viruses. In fact, this is a clear sign of neglect from the relevant stakeholders that should be quickly addressed, **especially with a focus on Africa**.

4. Unlike other infectious diseases such as malaria, influenza, neglected tropical diseases, and recently COVID-19, **studies that focus on the national and/or international frameworks and policies for controlling, eliminating or eradicating the disease are not available**. We attributed this observation to, possibly, the limited number of such frameworks and policies. Consequently, highly coordinated national and international response strategies and policies should be developed such that the entire African continent will pursue elimination and/or eradication campaigns.

5. Finally, our present review identified the **dearth of studies that project the socio-ecological,**

economic and psychological consequences of the disease such as a robust knowledge, attitude and practice (KAP) studies and other field-based qualitative surveys. These studies are highly critical and important for holistic strategic campaigns for controlling mpox virus in Africa.

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Authors' contributions
Conceptualization and study design: AAA.
Project administration: AAA, IAO.
Acquisition and analysis: AAA, IAO, OSA, TOF, TOS, MAA, SOT, WOS, MBI, GG, AOG.
Software applications: IAO, TOF, WOS, AOG, GG.
Data interpretation: IAO, TOF, AAA, OSA, TOS, MAA, WOS, MBI, AMM, EFH, RM, MAI.
Writing original draft: AAA, IAO, OSA, TOF, AM, TOS, JBN, OMM, ABD, MAA, SOT, ML, KNU, MAI, WOS, MBI, GG, AOG, AMM, EFH, IOA, RM.
Writing - review & editing: AAA, IAO, OSA, TOS, ABD, WOS, MBI, AOG, MAI, TOF, AM, JBN, OMM, MAA, SOT, GG, ML, AMM, EFH, IOA, RM, KNU.
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Declaration of Interest Statement
The authors declare that they have no competing interests.

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