NIGERIAN INFECTIOUS DISEASES SOCIETY

Review Article

The Implication of the Evolving Epidemiology of Human Monkeypox - Global and National Dimensions: A Narrative Review

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ABSTRACT

Background: Monkeypox was known to be an ignored disease, often reported from Africa, until recently when it attracted global attention due to multi-country surge in cases. This review is aimed at highlighting the implications of the changing epidemiology of the disease and identify related research gaps.

Methods: We conducted a detailed review of 46 relevant peer-reviewed, grey literature and relevant websites on the evolving epidemiology of monkeypox. The last search was performed on 30th June 2022.

Results: Cases of monkeypox has been on steady rise in some African countries since the first confirmed case in 1970, with most report from the Democratic Republic of Congo (DRC). Since 2003, import- and travel-related spread outside of Africa has occasionally resulted in outbreaks. Our review shows a recent Multi – country escalation of cases in non – endemic countries. Most of the existing literatures are on epidemiological report. There is dearth of interventional studies on biological behaviour of the virus, therapeutics and vaccination. The surge in cases after 40 years of caseation of smallpox vaccination, which provide cross- protection against monkeypox and growing median ages of cases from children to adults suggest wanning immunity. Risk factors include international travels and interactions/activities with infected animals or individuals.

Conclusions: Persistence of cases of monkeypox without intervention for over four decades in endemic countries and lack of support from global scientific community is responsible for the evolving epidemiology of monkeypox and multi-country outbreak. Global synergy is urgently needed to prevent and control the spread of the infection.

Key words: monkeypox virus, smallpox, outbreak, endemic.

INTRODUCTION

Monkeypox virus is an orthopoxvirus virus belonging to the Poxviridae family[1]. The causative agent of monkeypox infection was first isolated in 1958 among captive monkeys transported to Copenhagen, Denmark, from Africa[2]. Following the eradication of smallpox in 1979 via vaccination, it is regarded as the most critical human Orthopoxvirus infection[1,2]. Other human pathogenic orthopox virus species include the major variola virus, the causative agent of smallpox that was eradicated via vaccination in 1980, variola minor virus and cowpox virus[3].

Many animal poxviruses with zoonotic potential include the buffalopox virus, vaccinia, cowpox virus, and camel pox virus [1,3].

Monkeypox virus is typically a mild and self-limiting disease. However, it could rarely manifest as moderate and severe disease especially in immunocompromised and those with underlying comorbities[3,4].

Shortly after the first confirmed human case in 1970 involving a 9-year-old child in the DRC, the monkeypox has become endemic in DRC and has spread to other African countries mainly in Central and West Africa. The disease has persisted as an ignored and lingering health challenge for decades in Africa, until recently when it began to attract global attention due to multi-countries rapid surge in cases.

Recent epidemiologic reports from the endemic countries in sub-Saharan Africa, particularly in tropical and mangrove region Cameroon, the Central African Republic, Gabon, Cote d'Ivoire, Liberia, Nigeria, and Sierra Leone, shows that monkeypox is re-emerging[5,6]. In addition to the increase in cases of monkeypox infection, there is the expansion of the geographic distribution of human monkeypox within the endemic West and Central Africa. The appearance of cases from traditional non -endemic countries without an epidemiologic link to endemic region strongly suggest unidentified natural or animal reservoir[5.6]. It is also possible that monkeypox virus might have been circulating below levels detectable by the surveillance systems and sustained human-to-human transmission might have been undetected for a period of time. Other possible factors responsible for the rising cases in Africa include increased interaction between human and animal reservoirs due to exploitation of the environment, increased population, migration and genetic evolution of the virus and transmission dynamics of the disease[7]. Other possibilities include climatic and ecological factors facilitating changes between geographic areas and virus as an etiological factor for human disease. Most recent cases of confirmed human monkeypox involve individuals aged ≤ 40 years with a median age of 31 years. Individuals born after the global eradication of smallpox and the stoppage of its vaccination 40 years ago lack cross-protective immunity conferred by smallpox vaccination against monkeypox infection[5-7].

The current Multi-country monkeypox outbreak is characterised by sudden and unexpected appearance and wide geographic spread of cases. Since 1 January and as of 30 June 2022, 3413 laboratory confirmed cases and one death have been reported to WHO from 50 countries / territories in five WHO Regions[8]. The majority of laboratory confirmed cases (2933 /3413; 86 %) were reported from the WHO European Region. Other regions reporting cases include: the African Region (suspected / confirmed cases; 73/3413, 2%), Region of the Americas (381/3413, 11%), Eastern Mediterranean Region (15/3413, <1%) and Western Pacific Region (11/3413, <1%). One death was reported in Nigeria in the second quarter of 2022[8]. This narrative review is aimed at highlighting the implications of the changing epidemiology, implication of ignoring a potentially infectious disease by global scientific society, identify Monkeypox related research gaps that need to be explored to halt the ongoing Multi-country outbreak and call for and expedient, and coordinated global response against monkeypox.

METHODS

The information presented were obtained through detailed review of relevant peer-reviewed articles and grey literatures. Searches were performed in MEDLINE (accessed using PubMed), Embase, the Internet Library sub-Saharan Africa (ilissAfrica), Google Scholar, Ovid and African Journals Online (AJOL).

Published literatures on monkeypox from 1958 to 2022, and /or reported through 30th June, 2022, the date of last search, was considered for eligibility. In PubMed, searches included Medical Subject Headings (MeSH) and limits to title and abstract (tiab). The search string used in PubMed was Monkeypox [MeSH] OR "Monkeypox virus "[MeSH] OR monkeypox [tiab] OR “monkey pox” [tiab] and in Embase was ’monkeypox’/exp OR ’monkeypox virus’/exp OR monkeypox: ti,ab OR "monkey pox ":ti,ab . In AJOL and illissAfrica, separate searches were conducted for each Monkeypox and Monkeypox virus.

Ninety-seven articles that contained the relevant data for the review objectives were considered. We excluded non-human studies, modelling studies that did not provide original data, articles that focused primarily on smallpox, and articles with data not related to the topics of interest. The most recent article was considered from articles with similar results from largely identical data sets. In some instances, there was a partial overlap of results, such that different articles included the same cases plus some unique cases. In these situations, only the unique cases in each article were included. References were also reviewed to extend the search. In addition to the primary search sources, seven sources of grey literature and Google were searched with emphasis on the geographical spread of Multi -country outbreak of Monkeypox. These sources were the websites of the World Health Organization (WHO), specifically a review of the Weekly Bulletins on Outbreaks and other Emergencies, United States Centers for Disease Control and Prevention (CDC), Africa CDC, Nigeria CDC, African Field Epidemiology Network, Epicentre, and ProMed. The Google search was performed on the African countries known to have monkeypox cases, including a check on the websites of their Ministries of Health. After extensive review, 46 articles with an updated data on human studies, geographical spread of monkeypox were considered.

Monkeypox Virus Discovery and Animal Reservoir

The monkeypox virus was first detected in 1958 in an outbreak of a vesicular disease among captive monkeys transported to Copenhagen, Denmark, from Africa for research purposes[1,2]. Besides monkeys, other reservoirs, including rodents, striped mice, dormice, squirrels (rope and tree), and giant pouched rats that are hunted for meat in several regions of Africa, have been identified[2,3]. The extent of a wild animal reservoir, natural history and pathogenesis of monkeypox remains unclear. Therefore, detailed ecological and epidemiological studies of the geographic distribution of the animal host reservoirs are required. This can be achieved through an epidemiologic survey aimed at serological tests, genetic sequencing and viral isolation of the virus in rodents, small mammals, primates and wildlife to identify the animal reservoir, natural and incidental hosts of the human monkeypox virus[2,10].

Factors thought to be responsible for the increase in cases include waning cross -protective immunity among the population after smallpox vaccination was discontinued in the early 1980s and an increasing proportion of the non-vaccinated younger age groups[11,12]. Smallpox vaccination has been shown to confer cross-immunity against monkeypox. For instance, the proportion of the Nigerian population estimated to have been vaccinated based on statistical modelling in 2016, a year before the monkeypox outbreak in the country, showed that only 10.1% of the population was vaccinated[13]. The population immunity, which predicted waning individual-level immunity, was 2.6 %, a decline from 65.6% in 1970. By 2018, the vaccinated population had decreased to 9.3%, and the estimated population immunity had declined to 2.2%. This meta-analysis indicated that approximately 80–95% of monkeypox cases are unvaccinated against smallpox[13]. Another factor that may be driving the resurgence of monkeypox is the genetic evolution of the monkeypox virus. An analysis of 60 samples for genomic sequencing and analysis from primary and secondary cases of infection from Sankuru District, DRC, led to the detection of four distinct lineages within the Central African clade and revealed a gene loss in 17% of the samples that seemed to correlate with human-to-human transmission[14]. Increased contact between humans and small mammals that are potential reservoirs for the virus during forest and jungle exploration, natural disaster, civil unrest, refugee displacement, farming, increase in population, climate change and expanding ecological niche is a possible factor fuelling the rising cases in endemic countries[5-8].

Epidemiology of monkeypox prior to the current Multi -country outbreak

The index case of human monkeypox was identified and characterised as a distinct infection on September 1 1970, involving a 9-year-old child in The Democratic Republic of the Congo (DRC)[15]. Shortly after the initial confirmed case, six additional cases were detected between October 1970 and May 1971 from Liberia, Sierra Leone and Nigeria[7-10,15]. Prior to the current Multi–country outbreak, the disease was largely restricted to the countries in Central and West Africa, with DRC reporting most cases. Report of the number of cases per decade indicate that from 1970–1979, a total of 47 confirmed and probable cases were reported from six African countries, namely the DRC (n = 38), Cameroon (n = 1), Coˆte d'Ivoire (n = 1), Liberia (n = 4), Nigeria (n = 1), and Sierra Leone (n = 3), with most cases occurring in the DRC (n = 38)[17]. The number of confirmed and suspected cases reported from five African countries substantially increase to 356 from 1980–1989, with a 9-fold rise in DRC (n = 343), Cameroon (n = 1), Coˆte d'Ivoire (n = 1), Central African Republic (n = 8) and Gabon (n = 8)[6,9,13,17]. Cases continued to surge from 1990 - 1999, with 511 confirmed, probable, and/or possible monkeypox cases reported in DRC and 9 confirmed cases in Gabon[17].

From 2000–2009, DRC reported 10,027 confirmed and suspected cases, other countries that reported within the same period are Congo (n = 73) and South Sudan (n = 19). between 2010 and 2019, cases were found in seven African countries (Cameroon; 3, CAR; 61, DRC; 18,788, Liberia; 6, Nigeria;181, Sierra Leone;2, and Republic of the Congo;24)[6 ,13,17]. The evolving epidemiologic report of the monkeypox outbreak in endemic Central and West African Countries especially in DRC is characterised by a dramatic escalation in the number of cases[8,13]. A study conducted in DRC revealed that the surge in cases during the period was due to an actual increase in cases rather than active case search or improved surveillance, as the reporting system was uninterrupted by 2008[17]. In Nigeria, cases increased exponentially from 3 cases in the 70s[4,15] to 181 cases in 2017 – 2019[16].

In 2003, the first monkeypox outbreak outside of Africa was reported in the United States of America and was linked to contact with infected pet prairie dogs[18]. These pets had been housed with Gambian pouched rats and dormice that had been imported into the country from Ghana. This outbreak led to over 70 cases of monkeypox in the US[18]. Monkeypox has also been reported in travellers from Nigeria to Israel in September 2018[19], to the United Kingdom in September 2018[20], December 2019[21], May 2021[22], to Singapore in May 2019[23], and to the United States of America in July and November 2021[26].

Epidemiology of current Multi-country Monkeypox Outbreak

The current Multi-country monkeypox outbreak is characterised by sudden and unexpected appearance and wide geographic spread of cases. Countries outside African region that were not known to be endemic to monkeypox virus are reporting cases. Epidemiological investigation from most traditionally non–endemic countries shows that most reported cases thus far have no established travel links to endemic areas. The current cases reported from non - endemic countries are mainly but not exclusively identified amongst men who have sex with men (MSM)[8]. Further studies are necessary to ascertain if the monkeypox virus is transmissible via sexual intercourse. Prior to this Multi-country monkeypox outbreak, identifying confirmed and suspected monkeypox cases with no direct travel links to an endemic area represent a highly unusual event[8,27]. Since 1 January and as of 30 June 2022, 3413 laboratory confirmed cases and one death have been reported to WHO from 50 countries/territories in five WHO Regions. The majority of laboratory confirmed cases (2933/3413; 86%) were reported from the WHO European Region. Other regions reporting cases include: the African Region (73/3413, 2%), Region of the Americas (381 /3413, 11 %), Eastern Mediterranean Region (15/3413, <1%) and Western Pacific Region (11/ 3413, <1%). One death was reported in Nigeria in the second quarter of 2022[8,20-26]. The situation is evolving, and there is a possibility that more cases of monkeypox will be identified as surveillance expands in non-endemic countries.

Current evidence revealed that the strongest risk factor for contracting the disease is a physical contact with a person with symptomatic monkeypox infection[27,28].

One of the major reasons fuelling the ongoing Multi-country outbreak includes poor characterisation of both animal and natural reservoir of the monkeypox virus, neglect of the persisting cases in endemic countries by international communities, dearth of diagnostic facilities in endemic region, poorly coordinated surveillance. Vaccination against smallpox has been shown to boost immunity and protect against monkeypox[8,17-20,24] The unusual rising cases could be due to community transmission and or changes in the biological behaviour or genetic evolution of the monkeypox virus[8,16,17,19,24]. Rolling out effective monkeypox vaccines is critical in eradicating or curbing monkeypox, particularly in vulnerable populations such as young populations, those with immunosuppression or immunosuppressive drugs, health workers and contacts of cases[11,12]. The median age at presentation has evolved from young children (4 years old) in the 1970s to young adults (21 years old) in 2010[8,13,24-26].

The implications of persisting cases of monkeypox in endemic countries

Since the first reported case of Monkeypox in DRC over four decades ago, little or no attention was given to the disease by scientific community before the ongoing Multi-country outbreak. It was largely seen as a disease that is restricted to sub-Saharan African countries, particularly those located in tropical and mangrove regions of Central and West Africa[5]. An exponential increase is being reported from endemic countries particularly in DRC, which has spread to other regions of Africa (primarily West and Central), and cases outside Africa have also emerged in recent years. Countries that are known to be endemic for monkeypox include Benin, Cameroon, the Central African Republic, the Democratic Republic of the Congo, Gabon, Ghana (identified in animals only), Ivory Coast, Liberia, Nigeria, the Republic of the Congo, Sierra Leone, and South Sudan. The DRC recorded a 20-fold and 4-fold increase in incidence between the 1980s and 2006–07; and between 2001 and 2013, respectively[17]. Recently an exponential rise in cases has been observed in DRC as 1284 cases were reported within four months (1st January – 30th May 2022); other cases with a surge in cases include Cameroon 25 (December 15, 2021 – February 22, 2022), Central Africa Republic 6 (March 4 – April 10, 2022) and Nigeria 558 (September 2017 to December 2021).

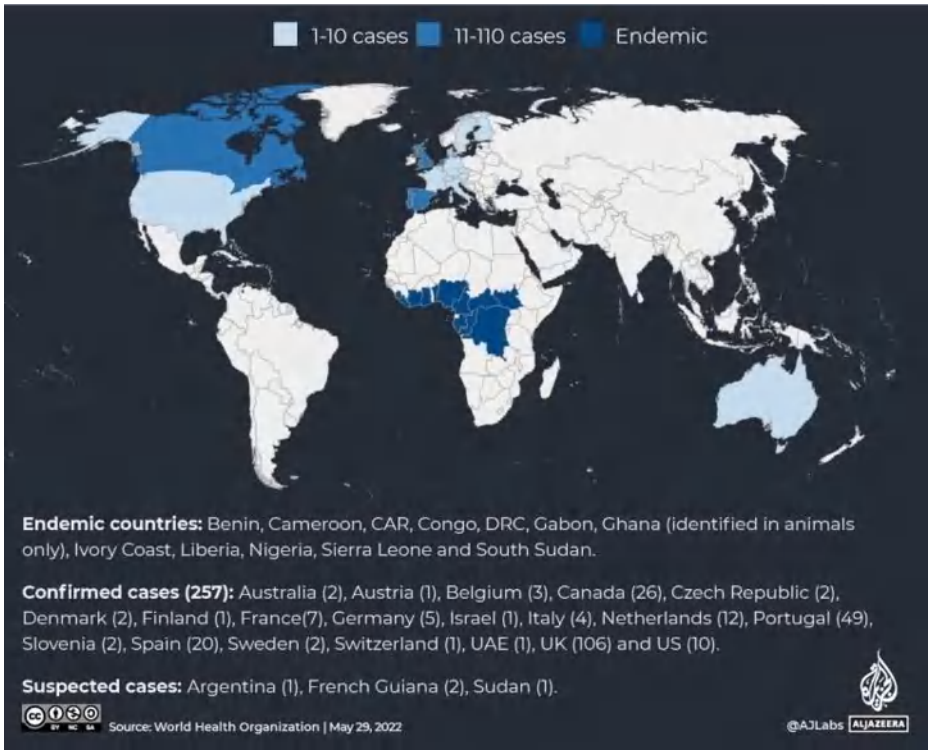

Fig 1. Global distribution of confirmed and suspected cases of monkeypox (source WHO, 2022)[8]

Figure 2; shows Monkeypox endemic countries in sub-Saharan Africa. Several sporadic clusters and cases of human monkeypox outside Africa but epidemiologically linked to endemic countries, especially Nigeria, have been reported.

Fig. 2: Monkeypox endemic African countries (Source WHO, 2019)[9]

Non-endemic countries reporting monkeypox cases are as shown in Figure 3. In 2003, a rat imported from Ghana infected co-habitant prairie dogs and subsequently resulted in fifty-three human cases of monkeypox in Midwestern United States[18]. In October 2018, one case was reported in Israel involving a man who travelled from Nigeria to Israel[19]. In May 2019, one case occurred in a man who travelled from Nigeria to Singapore[23]. In May 2021, three members of a family in the UK who returned from Nigeria became infected with the monkeypox virus. In July 2021, one case involving a man who travelled from Nigeria to Texas was reported. In November 2021, one case occurred in a man who travelled from Nigeria to Maryland. As of May 2022, contacts of a human monkeypox case in a man who returned to Massachusetts from Canada are under investigation, as well as clusters of human monkeypox in the United Kingdom [8,27,28].

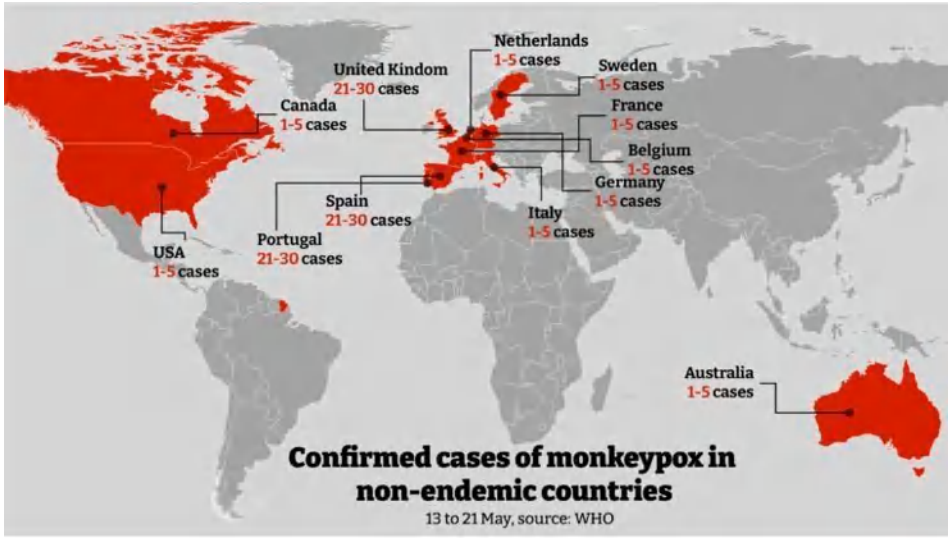

Fig. 3: Distribution of cases of monkeypox in non – endemic countries (Source: WHO, 2022)[18]

The re-emergence of the disease and expansion of geographical reach within the African region and explosion of cases outside traditional endemic region is as a result of decades of neglect and lack of coordinated response to prevent or control the spread of the disease. The implication of the Multi-country monkeypox outbreak is that ignoring an infectious disease in one locality or region constitute a health threat to global community.

Epidemiology and Spatiotemporal Distribution of human monkeypox in Nigeria

The first Human monkeypox case in Nigeria was reported in 1971, involving a four-year-old girl resident of Ihie-Umduru village in the present Abia State in the south-eastern region. The mother of the index case subsequently developed the disease, presumed to have contracted the virus from her child[29]. The third case occurred in 1978 in a thirty-five-year -old-man living in Omifunfun in the Oyo State in southwestern Nigeria.

Of the ten suspected cases between 1971 and 1978, only three were confirmed, and there was no fatality[30]. After almost four decades of no reported case, human monkeypox re-emerged in September 2017 in an eleven–year–old patient in Bayelsa State in the south southern geopolitical region which manifested with features consistent with the disease[31].

Within four months (September–December 2017) of the re-emergence of the disease, 88 confirmed cases were reported from 13 States of the three southern and northcentral geopolitical regions[8,16,24]. From September 2017 to 19th June 2022, a total of 674 suspected and out of which 267 confirmed cases of monkeypox were recorded from 33 states spread across all the geopolitical regions of Nigeria[24]. Of the reported cases, 267 (39.6%) have been confirmed in 23 states - Rivers (55), Bayelsa (47), Lagos (38), Delta (32), Cross River (16), Edo (13), Imo (10), Akwa Ibom (7), Oyo (7), FCT (8), Plateau (5), Adamawa (5), Enugu (4), Abia (3), Nasarawa (3), Benue (2), Anambra (2), Ekiti (2), Kano (2), Niger (2), Ogun (2), Ebonyi (1) and Ondo (1). In addition, from September 2017 to June 19th, 2022, a total of nine (9) deaths have been recorded (CFR= 3.4%) in six states - Lagos (3), Edo (2), Imo (1), Cross River (1), FCT (1) and Rivers (1)[8, 16,24]. (Figure 4; Map of Nigeria showing states reporting monkeypox).

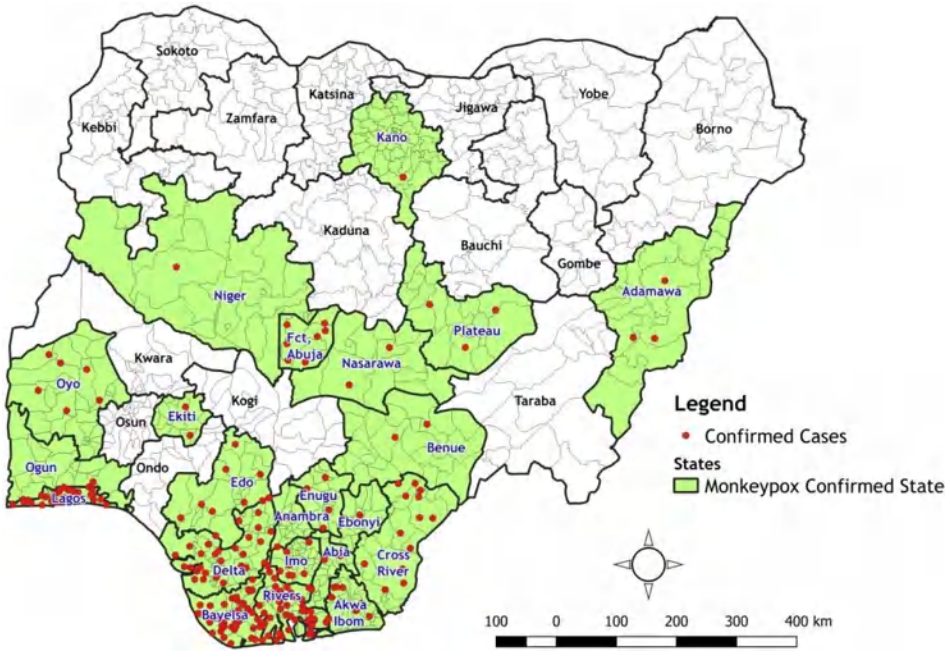

Fig. 4: Map of Nigeria showing the distribution of states reporting Monkeypox (Source: NCDC, 2022)[24]

One hundred and sixty-two suspected cases have been reported between January 1 and June 19, 2022. Of the suspected cases, 41 were confirmed from nine (16) states – Lagos (8), Adamawa (5), Bayelsa (4), Delta (3), Edo (3), River (3), Cross River (2), FCT (2), Kano (2), Imo (2), Plateau (2), Nasarawa (1), Niger (1), Oyo (1), Ondo (1) and Ogun (1). One death was recorded in a 40-year -old man with co-morbidity that was receiving immunosuppressive drugs[16,24]. The twenty (20%) new suspected cases in May 2022 were reported from 11 states – Lagos (5), Bayelsa (2), Adamawa (2), Rivers (2), Niger (2), FCT (2), Delta (1), Oyo (1), Kaduna (1), Edo (1), and Gombe (1). This is a 100 % increase in the case reported compared to April 2022, when ten new cases were reported, and is likely due to ongoing efforts to increase awareness and improve surveillance. The six (6) new confirmed positive cases (out of the 20 suspected cases) in May 2022 were confirmed from four (4) states – Bayelsa (2), Adamawa (2). Lagos (1), and Rivers (1)[24].

After the spike in cases at the beginning of the ongoing resurgence of monkeypox in the last four months of 2017 in Nigeria, the spatiotemporal distribution of cases remained uniform, implying that there is no seasonal variation in the transmission of the infection. Most monkeypox cases in Nigeria affect persons aged 40 years and below with a male preponderance. The higher proportion of male cases may be due to a higher risk of exposure to natural habitats and reservoirs of monkeypox than females. The monkeypox virus is expanding its geographical reach in Nigeria; prior to 2019, cases of monkeypox were restricted to the southern region. Since 2020, it has also extended to the northern part of the country[16,18,24].

Transmission Dynamics of Human Monkeypox Infection

The spectrum of the monkeypox virus's natural and animal reservoirs is uncertain; isolation of the virus from primates such as tree squirrel, rope squirrel, Gambian pouched rat and sooty mangabey monkey is a pointer to African rodents as reservoir species [32]. Most of the recently reported cases of monkeypox are from mangrove and tropical rainforest region that is home to abundant species of rodents, small mammals and primates. Human to human transmission has been shown to occur via respiratory droplets, contact with skin lesions and body fluids of an infected person. Contact with contaminated fomites such as clothes, linens or items used could result in inter-human transmission. Zoonotic transmission often occurs via direct contact while handling or consuming an infected animal reservoir. Similarly, zoonotic transmission is also possible from an infected animal through direct contact with blood, body fluids, and inoculation from mucocutaneous lesions. Definitive confirmation of human–to–human transmission in endemic areas is cumbersome as the primary, secondary and tertiary cases may have been exposed to infected animals.

The human monkeypox consists of two genetic clades, West African and the more virulent Congo Basin clade (Central Africa clade), often implicated in inter-human transmission[33]. Human transmission from an index case, secondary attack rates and serial transmission events from contacts have been demonstrated to be higher in Central Africa than in West African clade[33,34]. The virulence and higher attack rates for Central African clades are evident by the estimated reproduction number R0 in the range of 0.6 - 1.0[34,35,36]. The West African clade usually manifests with milder disease, fewer deaths, and limited human-to -human transmission. Congo Basin clade has reported mortality at about 10%, whereas the West African clade usually displays fatal outcomes in less than 1% of cases, although, this was observed to be much higher in HIV patients[35]. The pooled case fatality rate for the Central African clade obtained from Meta-Analysis was 10.6% versus 3.6% for the West African clade[36.] The implication of the high R0 in the Central African clade is that an outbreak due to it is capable of causing sustained inter-human transmission and persistent community transmission[36]. Conversely, a large outbreak due to the West African clade with presumed lower R0 is likely to be due to spillover from zoonotic hosts than sustained human -human transmission or community transmission. Sexual transmission has been postulated from an infected sexual partner with groin and genital lesions. The possibility of sexual transmission is still being evaluated. Nosocomial transmission has been described. Case (s) of human–to–animal transmission is yet to be reported[33-36].

Clinical Manifestation of Monkeypox Infection

The clinical manifestation of human monkeypox infection is similar to that of smallpox in terms of onset of symptoms, the timing of rash occurrence, and rash distribution, but generally less severe than smallpox in terms of complication rate, case fatality rate, and levels of scarification [37,38]. After an incubation period of 6−13 days (range 5−21 days), the infection often manifests as an initial febrile syndrome associated with generalised headache and fatigue. This syndrome is accompanied or occurs concurrently with rashes. The typical monkeypox rash appears as an indurated and depressed centre (umbilicated) lesions, which commonly begin from the face, head and upper body parts. It then rapidly progresses to involve the limbs and lower parts of the body[37,38]. The cutaneous/skin lesion rapidly progresses from macular lesions, papules, vesicles, and pustules and then forms crusts which dry up and fall off within two to four weeks.

The associated enlarged lymph nodes are firm, tender, and occasionally painful. However, there are reports of atypical presentation of the lesions starting from the genital area. Regression of the fever coincides with or up to 3 days after rash onset[37,39,40]. Lymphadenopathy is often seen in monkeypox, but it was not characteristic of smallpox. Most immunocompetent adult patients manifest mild, self-limiting illnesses. Others may be asymptomatic. The clinical course tends to be more severe in immunocompromised individuals and children[36-38].

Clinical and epidemiological factors, including assessment of the likelihood of infection from contacts of the case(s), need to be considered in the initial evaluation of cases [37]. Due to a wide range of conditions that manifest with skin rashes and atypical presentation during large outbreaks, it can be challenging to differentiate monkeypox solely based on the clinical presentation, particularly for cases with an atypical presentation[37,38]. It is therefore essential to consider other potential causes of discrete skin lesions or a disseminated rash; Examples of other conditions known to cause similar-appearing skin lesions at the different stages of development include measles, molluscum contagiosum, Treponema pallidum (syphilis), herpes simplex virus, varicella zoster virus, virus, enterovirus, scabies, chancroid. Bacterial skin infections, medication allergies, and parapoxviruses[36-38].

Diagnostic Challenges of Detecting Monkeypox Virus in the Endemic Region

Diagnosis of the monkeypox virus is confirmed by the identification of the virus by polymerase chain reaction (PCR). Relevant clinical, epidemiological and vaccination information are necessary. The representative sample obtained from skin lesions such as swabs from vesicular lesions, crusts or exudate, oropharyngeal or nasopharyngeal swabs, skin biopsies of vesiculopapular rash or samples of the roof of an intact vesicular lesion are appropriate for laboratory analyses. Obtaining lesion exudate on a swab or crust specimens is valuable and least invasive acute patient specimens when sample storage facilities are limited or absent. The test is done in accredited biosafety level-three facility or reference laboratory with high containment facilities. Case detection, surveillance, and access to timely and accurate laboratory testing of samples from cases under investigation of this emerging infection remain a huge challenge in most endemic countries in Africa. Laboratory testing methods and algorithms should be developed, standardised and validated PCR protocols for detecting orthopoxvirus (OPXV) and, more specifically, monkeypoxvirus (MPXV), some of which include the distinction of Congo Basin and West African clade should be adopted.

Monkeypox viral infection is established through the nucleic acid amplification test (NAAT). The NAAT utilises either real-time or conventional polymerase chain reaction (PCR) for the detection of unique sequences of viral deoxyribonucleic acid (DNA). The PCR can be used for amplification or in combination with sequencing. Several groups have developed validated PCR protocols for the detection of orthopoxvirus and, more specifically, monkeypox virus, some of which include the distinction of Central African (Congo Basin) and West African clades[39-43] The investigation protocol involves two steps; the first PCR reaction detects orthopoxvirus. The second step involves PCR-based or utilises sequencing, to specifically detect orthopoxvirus species. Positive detection using an orthopoxvirus PCR assay followed by confirmation of monkeypox virus via PCR and/or sequencing or positive detection using monkeypox virus PCR assay in suspected cases in endemic and non-endemic areas indicates confirmation of monkeypox virus infection.

It is preferable to perform monkeypox virus-specific confirmatory testing. However, a positive orthopoxvirus PCR assay suffices for confirmation of suspected cases in non-endemic countries. Member states are expected to share and notify World Health Organisation (WHO) of laboratory-confirmed cases promptly. When the clinical presentation and epidemiology suggest an infection with the monkeypox virus despite negative PCR results, serological testing may be useful to trace prior infection for epidemiological purposes. A number of factors could contribute to false-negative results, such as wrong handling and preservation of specimen, shipping, or technical reasons inherent to the test, e.g. DNA extraction failure[41,43,44].

Therapeutic Options and Vaccines

There is currently no specific treatment for human monkeypox. Supportive care and aggressive treatment of complications are the cornerstones of effective management. Several antiviral drugs, such as Cidofovir and Brincidofovir (CMX 001), have proven anti-monkeypox viral activity in vitro and animal studies[45]. Tecovirimat (previously known as ST-246), an oral antiviral agent, has in vitro activity against the monkeypox virus, but its efficacy and safety in humans are still being evaluated[46]. There is currently no commercially available vaccine specific to monkeypox. ACAM2000, a smallpox vaccine that contains live Vaccinia virus, has been shown to confer 85 % from monkeypox infection. Other investigational vaccines include Aventis Pasteur Smallpox Vaccine (APSV), which contains a replication-competent Vaccinia virus and Imvamune (MVA-BN). Unlike ACAM 2000 and APSA, Imvamune could be administered to individuals with certain immune deficiencies[47].

The vaccine, LC 16 m8, which also contains attenuated vaccinia virus and has fewer adverse effects than ACAM 2000 has been licensed in Japan. ACAM 2000, which contains live Vaccinia virus confers 85% protection from monkeypox infection. It is recommended for frontline health workers and those exposed to patients' sample or body fluids from lesions. LC16m8 prevent viral replication and has shown protection against severe monkeypox illness in non-human primates. An ideal vaccine for use in monkeypox-endemic is those with good safety profiles that can be given to all age groups, including children and occupational risk groups. No vaccination meets all of these criteria, but some next -generation vaccines show the prospect of achieving this goal[46-48].

Vaccinia Immune Globulin (VIG) which is obtained from pooled blood of individuals who have been inoculated with the smallpox vaccine contains in antibodies against Vaccinia virus. There is no available data on the effectiveness of VIG on the prevention and treatment of complications from monkeypox infection, however its use may be considered in patients with severe infection[49]. The CDC recommends the prophylactic use of VIG in persons who have been exposed to the virus but have severe cellular immunodeficiency with contraindication to smallpox vaccination[50].

Summary of Implications of the Evolving Epidemiology of Monkeypox

1. Monkeypox infection is gradually evolving and attracting global relevance and attention.

2. The waning individual and herd immunity due to the stoppage of smallpox vaccination may be partly responsible for the global resurgence of monkeypox.

3. The unusual rising cases could be due to community transmission and /or change in the monkeypox virus 's biological behaviour or genetic evolution.

4. Reporting cases from traditional non-endemic countries without the epidemiologic link to endemic regions strongly suggests inter-human transmission from local unidentified natural or animal reservoirs.

5. The observed clusters of monkeypox infection among men who have sex with men may be due to contact with fluid from lesion, however the possibility of sexual transmission need to be elucidated

6. Lack of monkeypox infection detection tests, weak surveillance in endemic countries, and poor understanding of the evolution of the disease's clinical features and transmission dynamics are contributing to widespread human transmission of the virus.

7. Access to an effective monkeypox vaccine is critical for eradicating or controlling the infection, particularly in vulnerable populations such as the young population, those with immunosuppression or immunosuppressive drugs, health workers and contacts of cases.

Conclusion

The appearance of Monkeypox outside Africa is attracting global relevance and attention. The evolving epidemiology of Monkeypox that is responsible for the Multi -country outbreak is due to age long lingering cases in endemic countries and lack of support from global scientific community. Ignoring a potentially infectious disease in a locality or region has a potential for Multi- Country spread and serious global public health implication.

Recommendations

There is an urgent need to halt the ongoing monkeypox outbreak from evolving to a pandemic through extensive research on transmission dynamics, characterisation of reservoirs and possible natural habitat of the virus, including possible genetic evolution of the virus. Other measures include provision of prompt laboratory testing; deployment of smallpox vaccine and treatments; development of guidance for patients, healthcare providers, veterinarians, and other animal handlers; tracking potentially infected animals; and investigation into possible human cases. Global synergy in risk communication, prompt case detection, surveillance, definitive diagnostics of cases, effective drug therapy and vaccines is urgently need to control the spread of the infection.

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