Molecular Aspects of the Monkeypox Virus and their Impact on the Virus's Change in Epidemiology

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Objective: Monkeypox is a viral zoonotic disease endemic to West and Central Africa; it has been reported in more countries during the last decade than in the previous 40 years. In 2022 a multinational outbreak occurred. This change in the epidemiology of the virus may represent an evolutionary adaptation. The purpose of this study is to analyze the molecular aspects of Monkeypox virus (MPXV) disease that may explain the latter's change in epidemiology during the 2022 outbreak.

Methods: From July 2022 through December 2022, the period of the outbreak, a narrative review was conducted on the available literature, with a total of 271 articles published in the MEDLINE/PubMed and LILACS databases being examined. The chosen articles were organized using the search and reference manager Mendeley Desktop 1.19.4. Duplicates and articles that did not meet the study's objective were eliminated, resulting in the selection of 49 articles for the present review.

Discussion: MPXV resurgence poses challenges due to waning immunity and changing epidemiological patterns. Recent outbreaks show different transmission routes, affecting new demographics. Genomic evolution, vaccination history, and potential new animal reservoirs complicate containment efforts. Continued surveillance and vaccination are crucial for control.

Conclusions: It seems possible that MPXV has (re-)emerged to occupy the ecological niche left by the smallpox virus. Mutations of the apolipoprotein B mRNA editing enzyme, catalytic subunit 3G motif, in MPXV clade IIb since 2017 may explain the epidemiological change that has occurred in recent years. This pattern could be due to sustained transmission in a new host or a new route of infection.

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The monkeypox virus (MPXV) is a poxvirus belonging to the genus *Orthopoxvirus* (OPV), which includes the camelpox, cowpox, vaccinia, and variola viruses. It is the most important OPV affecting human populations since the eradication of smallpox in 1980 (1). A self-limiting zoonotic viral disease found primarily in people residing in areas adjacent to tropical rainforests in Africa, MPXV is transmitted primarily through the blood, bodily injury, fluids from infected animals, the shedding of viral particles through the feces, and the exchange of contaminated items (2). However, on 23 July 2022, the World Health Organization (WHO) declared a multinational outbreak of monkeypox due to an increase in cases and because the clinical features differed from those previously described in African outbreaks. According to early reports, most of the cases were linked to transmissions that had occurred primarily among men who have sex with men (MSM) (3). According to data, as of 11 November 2022, the total number of confirmed cases amounted to about 65,000, with Spain and France being the most affected countries in Europe (4).

While this is not a new disease, such a rapid series of MPXV infections has not been experienced in either Europe or America since the detection of the first human case in 1970. Reports of the disease were generally sporadic, with Nigeria reporting 10 human infections from 1971 through 1978 (5), while cases outside the African continent were unusual. However, from September 2017 through June 2021, there were 466 suspected cases, of which 205 were confirmed, with 8 deaths reported (6). Thus, human monkeypox has been reported in more countries in the last decade than was the case for the 40 years prior to it (7), making it the most prevalent orthopoxviral infection in humans.

Against this backdrop, the new clinical features observed in the 2022 outbreak make it essential to analyze genomic studies in order to understand the likely evolutionary adaptations of the virus, as analyzing the genome sequences of reported MPXV isolates through phylogenomics allows us to determine the prevalences of the different mutations and and the evolutionary dynamics of the virus, itself . The present research, then, aimed to analyze those molecular aspects of MPXV disease that may explain the change in epidemiology that occurred during the outbreak in 2022.

Methods

A narrative review of the available literature was conducted from the start of the multinational outbreak of MPXV in July 2022 and extending through December 2022. The sources of information consulted were the MEDLINE/PubMed and LILACS

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databases, without language restrictions. A secondary search was also conducted for reports from the WHO, the US Centers for Disease Control and Prevention, and the Nigerian Centre for Disease Control. The search and analysis of the information were performed in a customized time range (2017–2022), using MeSH (Medical Subject Headings) linked to free terms: monkeypox, viral zoonoses, communicable diseases, emerging, disease outbreaks, monkeypox/epidemiology, animals, and molecular mechanism. The search strategy employed consisted of reading and critically analyzing the methodology, results, and discussion sections of the articles and reviewing the molecular aspects and epidemiology of MPXV. In so doing, a total of 271 articles were consulted, which articles were organized in the search engine and reference manager Mendeley Desktop 1.19.4 to then eliminate duplicates and those articles that did not fit the objective of the study; 49 articles were selected for the present review, and they were evaluated during the period of November through December 2022 (Figure 1).

Development

Virology and genetic basis

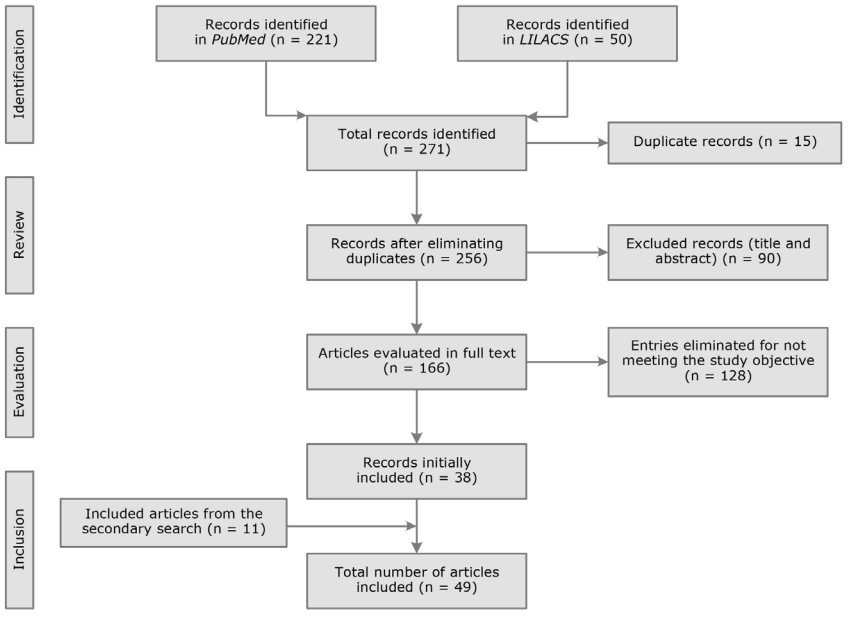
The monkeypox virus belongs to the family *Poxviridae*, subfamily *Chordopoxvirinae*, genus *Orthopoxvirus*. It is an ovoid or brick-shaped virus, 200–250 nm in length, enveloped by a geometrically corrugated lipoprotein outer membrane. The genome consists of a linear double-stranded DNA molecule of 196.44 (±3.42) Kb, with coding sequences of 188.57 (±10.43) Kb, and an average GC percentage of 33.06% (±0.06%) (8). Its natural hosts are mammals, including humans, whose viral cycle occurs in the cytoplasm of infected cells (dendritic cells, monocytes/macrophages, B-lymphocytes, activated T-lymphocytes). The binding of viral proteins to host glycosaminoglycans mediates endocytosis. There are 2 forms of infectious virions produced in infected cells: intracellular mature virus, which is released upon cell lysis, and extracellular enveloped virus, which can acquire a second membrane from the Golgi apparatus and bud from cells through interaction with actin tails, which may be the cause of the rapid spread of infection within an infected host (9,10).

Despite the clinical similarities of the diseases, MPXV is not considered the direct ancestor of the variola virus; rather, both viruses evolved from progenitor poxviruses that are more similar to the vaccine pox virus lineage (11). Traditionally, MPXV is recognized as having 2 phylogenetically distinct clades: the Congo Basin (central Africa) clade and the West African clade, the latter being related to less severe MPXV infections in primates and humans (1,12). However, following the multinational outbreak in 2022, the phylogeny and nomenclature of the virus has been revised, so that its naming now involves the use of a Roman numeral for the clade and a lowercase alphanumeric character for the subclade. Thus, the Congo Basin (Central Africa) clade is now called clade one (I) and the West African clade, clade two (II); we use both forms of nomenclature interchangeably in this manuscript. In addition, it has been agreed that clade II consists of 2 subclades, IIa and IIb, the second of the 2 refers, primarily, to the cluster of variants that were predominantly prevalent during the global outbreak of 2022 (Figure 2) (13).

To explain the differences in virulence and transmissibility between the Congo Basin and West African clades, analyses have been carried out based on the genes that are likely to be responsible for these characteristics. The D14L gene encodes an enzyme called the monkeypox inhibitor of complement enzymes (MOPICE). This enzyme is related to a pair of complement enzyme inhibitor genes (smallpox inhibitor of complement enzymes and the virus complement control protein) of the variola and vaccinia viruses, respectively. The D14L gene has been found in Congo Basin isolates but not in any of the sequenced West African viruses. The lack of MOPICE in West African MPXV isolates could increase the susceptibility of virus-/virion-infected cells to host-derived complement-mediated lysis, contributing to reduced viremia, transmissibility, and disease severity (14). Other genes that are possibly important for the virulence and transmissibility of MPXV isolates from the Congo Basin are *D10L* (which inhibits interferon-1 signaling), *B10R* (virulence factor for myxoma virus), *B14R* (interleukin-1 binding protein), and *B19R* (serine protease inhibitor-1) (12).

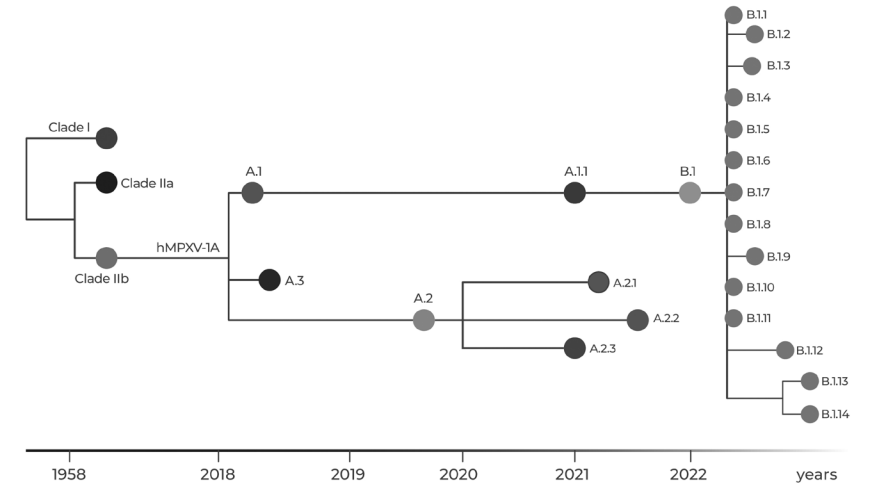
It is estimated that the Old and New World orthopoxviruses diverged approximately 40,000 years ago and that MPXV first appeared in the Old World orthopoxvirus clade about 3,500 years ago. Since then, it has evolved and further segregated into other genetic variants, such as the West African MPXV subtype, which dates back about 600 years (15). As mentioned above, MPXV is traditionally divided into 2 clades, with a subclade of the second being responsible for the current outbreaks outside Africa. The coding regions involved in a given host's

Figure 1. Information search and analysis flowchart



recognition of antigenic determinants (e.g., the glycoproteins B21R and H3L) form the primary distinctions between the clades (16). However, Happi et al. (17) proposed an alternative classification system for MPXV, dividing the virus into 3 clades (I, IIa, and IIb). This system of classification represents the historical discovery of MPXV and incorporates viral genomes from West African and Central African regions, as well as from indirect events that occurred in northern countries (Figure 2); these 3 clades represent a profound diversity of MPXV, having accumulated over many years of evolution in the animal reservoir (17).

Figure 2. Schematic representation of the monkeypox virus (MPXV) phylogeny. The appearance of the lineages is presented in sequential order of sampling date, including hMPXV-1A, which contains multiple lineages related to the international outbreak in 2022. Figure modeled after figures in references 18 and 21 and modified as needed



For its part, the Nextstrain platform has taken into account the work of Happi et al. (17) to unravel the genomic epidemiology of MPXV (18) and has agreed to name a new subclade of IIb, this one containing genomes sampled from 2017 through 2019 in the UK, Israel, Nigeria, the USA, and Singapore, as well as genomes from global outbreaks in 2022. As the viruses in this subclade have been transmitted from human to human in dozens of countries (possibly for several years), which represents a different transmission route than has been observed in earlier cases, the name hMPXV1 has been considered (Figure 2) (17).

To date, multiple lineages have been identified as arising from the hMPXV-1A clade, all of which belong to lineage A (the descendant lineages being A.1, A.2, A.3, and so on). As the first detected descendant lineage of A.1.1, the lineage associated with the international outbreak of 2022 would be delineated as B.1 (17). However, it should be noted that the B.1 lineage was also found (2018–2019) to cluster with cases associated with an endemic country and segregate on a divergent phylogenetic branch, possibly reflecting accelerated microevolutionary events (19). In fact, microevolution of the B.1 lineage is known to have formed several clusters, from B.1.1 to B.1.14, suggesting ongoing viral evolution (Figure 2) (20).

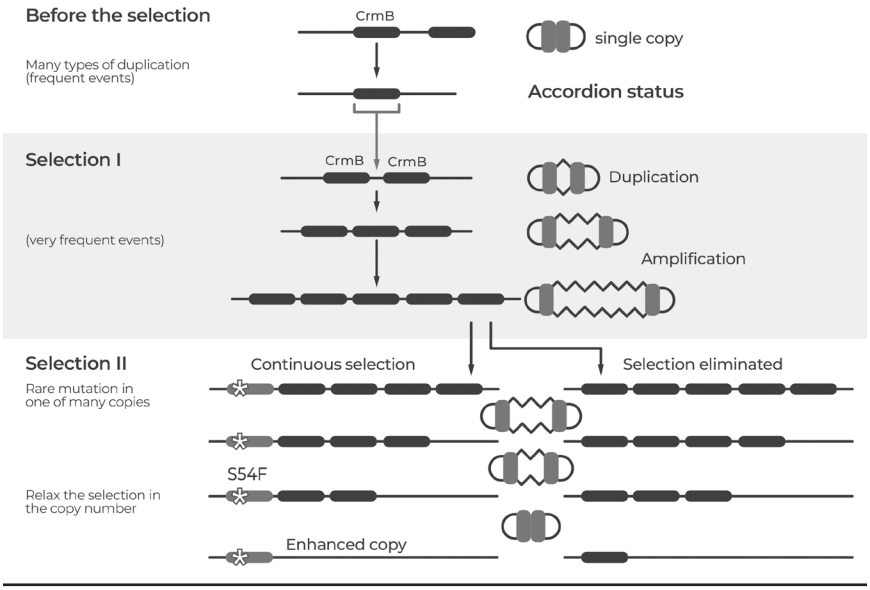
The majority of hMPXV isolates are from Central and West African countries, with the most important of them coming from the Democratic Republic of Congo, Israel, the USA, Singapore, and France. For the outbreak under discussion, the isolates obtained were MPX/UZ_REGA_1/Belgium/2022, MPX/UZ_REGA_2/Belgium/2022, MPXV_FRA_2022_TLS67, and MPXV_USA_2022_MA001 (8). Two of these isolates were reported from Belgium, 1 from France, and 1 from the USA, as indicated in their nomenclature. Based on the database of Kumar et al. (8), who recorded 71 isolates from 2005 through 2022, it has been determined that the largest genome size was observed for strain Sudan 2005_01 (206.37 kb), while the smallest was for strain MPXV-M5320_M15_Bayelsa (185.31 kb). Likewise, the highest number of coding sequences (open reading frames [ORFs], n = 219) was observed for strain MPXV_FRA_2022_TLS67, which was obtained from a male French patient in May 2022 (22) and had a genome size of 197.12 kb (8). In sum, of the 71 isolates reported in the database of Kumar et al. (8), 52 were isolated from *Homo sapiens*, and the rest from wild monkey, dormouse, Gambian rat, rope squirrel, and prairie dog, suggesting the potential of MPXV to infect a wide range of hosts.

Probable mechanisms of adaptation to the human host

Forty-six specific single nucleotide polymorphisms (SNPs) were found to pertain to the hMPXV B.1 lineage; these consisted of 4 intergenic, 18 synonymous, and 24 non-synonymous mutations, which mutations separated the clade from its closest reference sequence. Both B21R and H3L, immunogenic surface glycoproteins, are also thought to facilitate transmission (16); it is believed that 10 proteins are more prone to mutation, which was discovered by assigning mutations to the 187 ORFs of the MPXV genome, of which OPG210 and OPG105 have multiple nucleotide substitutions in MPXV-2022 strains and are mutated in multiple lineages (23). Tracing and predicting various aspects of the MPXV transmission dynamics could not be done based on random mutational events alone, but these mutations are very likely to be underlain by evolutionary mechanisms unique to orthopoxviruses. Thus, there are at least 4 pathways by which hMPXV may have acquired evolutionary adaptations so rapidly: sequence deletions, transient variations in genome size, genetic recombination, and specific mutations driven by the human enzyme apolipoprotein B mRNA editing enzyme, catalytic subunit 3G (APOBEC3).

Prior to the multinational outbreak in 2022, the evolutionary changes experienced by MPXV were mainly attributed to the progressive loss of genes at the terminal ends of the genome. Selective pressure from the host species might be responsible for accelerating the speed with which these changes occurred. In this regard, it has been described that variability is most evident in genes that are functionally involved in various virus–host interactions and are located near the terminal ends of the virus

Figure 3. Genomic accordion mechanism based on the variola virus K3L gene and adapted for the CrmB gene. The growth benefits of duplication and amplification cause exponential increases in CrmB gene frequency, making the final S54F mutation exponentially more likely. Figure modeled after a figure in reference 29 and modified as needed



genome, whereas the central region of the core genome encodes much more conserved genes involved in replication. That being the case, genome sequences that no longer render any kind of selective advantage in terms of viral replication might be deleted, providing a significant impetus for these viruses to evolve (24).

Furthermore, gene copy number variations with enhanced viral fitness for human infection and transmission would be possible through the generation of genomic accordions in poxviruses (Figure 3) (25,26). This second theory is based on the fact that rapidly diversifying host immune responses pose significant barriers to successful intra- and inter-species virus transmission, and many RNA viruses evade immunity with high mutation rates, short generation times, and large effective population sizes (27). However, DNA viruses, such as poxviruses, encode a wide variety of genes that hijack or antagonize host cell components that promote viral fitness (28). In this way, these mechanisms in turn promote viral evolution through transient variations in genome size.

To explain this phenomenon in detail, one study subjected the vaccinia poxvirus to serial propagation in human cells to assess the genomic changes it would undergo in response to protein kinase R (PKR), one of the most potent innate defenses against viruses and one that is poorly counteracted by the viral gene product K3L. In that way, the viruses quickly developed increased adaptability via repetitive enhancements of the K3L gene, resulting in expansions of genome size by as much as 7% to 10%. These necessary expansions were temporary and served to counteract human PKR, facilitating an adaptive amino acid substitution in K3L that also overcame PKR. While managing to preserve the adaptive substitutions, the innate costs of a larger genome size were offset by associated decreases in gene copy number (Figure 3) (25).

The common cytokine response-modifying protein B (*CrmB)* appears to be a key regulator in conferring on the simian pox virus a selective advantage against the host immune system. It binds tumor necrosis factor alpha (TNF-α) and TNF-β and thus protects infected cells by preventing TNF-mediated immune responses against viruses. The speed of *CrmB* adaptation in MPXV could be explained by there being mechanisms similar to those occurring in the K3L gene of the variola virus. Additional copies of the *CrmB* gene may confer on the virus a selective advantage against the immune system. As the accordion gene expands by adding copies of the *CrmB* gene, the amount of *CrmB* protein increases, whereas, if selection is relaxed, as occurs in a permissive host, the number of *CrmB* gene copies falls, i.e., the accordion contracts (Figure 3).

Duplications and subsequent amplification steps may occur at very high rates, as is the case with the *K3L* gene in the variola virus. The advantages of duplication and amplification in terms of growth provoke exponential rises in the prevalence of individuals within the population who carry amplifications. These amplifications in copy number exponentially increase the likelihood that subsequent mutations will occur. In this sense, the presence of the S54F mutation in the CrmB protein, which is common to all the recently documented monkeypox isolates, indicates that the selected strains may be adapting (8). It has also been documented that the S54F mutation can destabilize the structure of the *CrmB* protein (8), which could relax selection in amplification and allow the selective loss of the extra copies of the mutant gene due to the inherent cost of amplification. Thus, the genomic accordion mechanism could explain the presence of the S54F mutation, which is very common in the MPXV isolates from the 2022 outbreak (8).

While mutations in MPXV that may be contributing to its adaptation have been demonstrated, the main genetic mechanism of variability in poxviruses is genetic recombination, which can generate new phenotypes with greatly altered disease potential that are better adapted to viral survival. Viral DNA from poxviruses such as vaccinia has been shown to be exchanged about 18 times per genome in a single round of infection to produce recombinant phenotypes (30). Thus, given the evidence that MPXV has evolved rapidly over the last 4 years, it is necessary to consider that adaptation may be driven by recombination, which allows for more rapid gene copy number variation. For that reason, tandem repeats (TRs) and linkage disequilibrium (LD) have recently been studied in 415 MPXV viral sequences from 1 January to 20 July 2022 worldwide. The 2022 MPXV was divided into 4 lineages and 11 subgroups according to various TRs and their copy numbers. In addition, an analysis of LD demonstrated that virus evolution resulted in 3 new lineages, with 8 new recombinants (6 from Slovenia, 1 from Australia, and 1 from Italy) having been identified

using TR analysis, and 3 recombinants (2 from Germany and 1 from Spain) having been identified using LD analysis. The previous findings suggest that the simian pox virus diverged genetically during the 2022 pandemic (31).

A final mechanism that may explain the number of adaptive mutations that led to the multinational outbreak of MPXV in 2022 is APOBEC3, an intracellular innate defense mechanism. Links of this mechanism to the development of mutations in the virus emerged Upon analyzing the genome of simian pox cases from 2022, significant correlations between this mechanism and the development of viral mutations emerged. Approximately 50 genetic variances were identified compared to detected genomes (2018–2019). Notably, 3 amino acid alterations (D209N, P722S, and M1741I) were detected within the surface glycoprotein B21, which is a key immune target known for its role in virus evasion and immune transmission (19,32). Furthermore, 46 SNPs displayed a mutational bias, with 26 and 15 substitutions favoring GA > AA and TC > TT, respectively. This biased mutational pattern, in conjunction with the abundance of A:T bases in MPXV DNA, suggests the involvement of non-random enzymatic processes, potentially implicating factors such as APOBEC3 as drivers behind this extensive mutagenesisis behind this large number of mutations.

One of the DNA cytidine deaminase enzymes involved in mammalian antiviral defense is APOBEC3, which targets single-stranded DNA and cleaves cytosine to create uracil bases that are then paired with an adenine base. Sometimes APOBEC3 will not affect a virus enough to inactivate it, and said virus will continue to replicate and transmit but with alterations to its genome sequence resulting from the enzymatic attack. The involvement of APOBEC3 as an antiviral defense mechanism and mutation generator is documented in HIV infection, in which the expression of APOBEC3 increases markedly after infection (33). In a North American study, 2 MPXV lineages were identified between 2 cases from 2021 and 7 from 2022: the major variant from the 2022 outbreak, called B.1, and a minor variant sampled contemporaneously, called A.2. Mutation analyses of these 2 variants revealed an extreme preference for GA-to-AA mutations, indicative of human APOBEC3 cytosine deaminase activity (34).

Thus, it is very likely that this enzyme is responsible for adaptation to the human host and even facilitates cryptic transmission in HIV co-infected populations, as revealed in the study by Thornhill et al. (19), who observed that specific APOBEC3-driven mutations in HIV patients can further reduce the pathogenicity and symptoms caused by MPXV infection, thereby motivating adaptive evolution.

The role of APOBEC3 in the adaptive evolution of hMPXV is becoming increasingly well understood. We recently explored the abundance of G-to-A mutations in the APOBEC3 motif along the evolutionary trajectory from the common ancestor of the A lineage to the A.2 and B.1 variants and found a sequential acquisition of mutations in different individuals (sampled historically since 2017) that have contributed to the high proportions of APOBEC3 from GA to AA. Likewise, an analysis of 397 genomes from outbreaks sampled from 1 May to 15 July 2022 (available through the Global Initiative on Sharing All Influenza Data) confirmed the pattern observed in the first 12 sequences: 275/308 (89%) of the unique G-to-A mutations observed occurred in the context of APOBEC3. In contrast, G-to-A changes from the APOBEC3 context were lower than expected relative to other G-to-A changes in MPXV clade I and clade IIa. To better resolve where in the phylogeny the change in mutational patterns arose, we assessed mutational frequencies along internal branches in clade IIb leading to lineage A, and these were not found to be statistically enriched for G-to-A changes from the context of APOBEC3 (34).

Changes in epidemiology

One factor that has influenced the resurgence of MPXV is undoubtedly the genetic evolution of the virus. This has been the product of progressive change over the years, though, as already mentioned, the deletion of gene sequences may have played a part in this process. In support of this theory, an analysis of the genomic variability of MPXV obtained from 60 samples gathered from humans in the Democratic Republic of Congo (2005–2007) revealed the existence of 4 distinct lineages and a gene deletion (in 16.7% of samples) that appeared to correlate with human-to-human transmission ($P = .0544$) (35). Likewise, a new study indicates that in the years 1970 through 1989, MPXV was a disease that mainly affected young children with a median age at presentation of 4 to 5 years, which increased to 10 years of age from 2000 to 2009 and 21 years from 2010 to 2019. However, the epidemiological change would also have had an impact on the mortality of the virus, as 100% of the deaths during the first years of its discovery were in children under 10 years of age, while for the years of 2000 through 2019, children under 10 years of age accounted for only 37.5% of deaths (36).

Another important aspect in the changing epidemiology of the virus is the demonstrated risk factors for infection. In this regard, living in rural and forested areas of central and west Africa, handling and preparing bushmeat, caring for someone infected with MPXV virus, and not being vaccinated against smallpox all represented risk factors for acquiring endemic MPXV (37), whereas in all the studies prior to the 2022 outbreak, being male had already been linked to the risk of infection. This fact was attributed to the cultural norm that directs that men frequently hunt and have contact with wild animals (38). However, in the 2022 multinational outbreak, it was confirmed that the affected population was mostly MSM and that the disease's presentation involved genital lesions (39). This revealed a change in the presentation of these new cases.

Discussion

The resurgence of MPXV in recent decades reveals an unfavorable outlook for diseases of zoonotic origin. Reports of outbreaks in African countries and its re-emergence in Nigeria after almost 40 years (40), as well as sporadic outbreaks in Singapore (41), Israel (42), Maryland, USA, and the UK (43), until just before 2020, may be the result of waning immunity to the variola virus and deforestation. However, in May 2022, there was evidence of a notable increase in cases with epidemiological patterns different from those previously reported for the disease, with more than 80,000 cumulative cases as of November 2022 (44).

The development of MPXV in this new outbreak could be related to the immune status of the patients, as the presentation

of the cases is consistent with the cessation of routine antiviral vaccination in the 1980s after the disease's eradication (45). Thus, in the 2000s, only adults aged 20 to 25 years and older had a history of smallpox vaccination, leaving the under-20 age group vulnerable. Meanwhile, the median age of MPXV cases increased from 10 to 21 years in the next decade (36). In this sense, it is clear that the virus that appeared in 2022 presents different epidemiological patterns: In Spain in 2022, 99% of the cases of MPXV were found to have involved the MSM population, with the lesions predominantly affecting the genital, perineal, and/or perianal areas and with inguinal lymphadenopathy as a predominant feature, suggesting that the sexual route was the main mode of transmission (46). In addition, Germany reported 1,304 confirmed cases as of 6 July 2022, again, mostly in the MSM population (38).

Research into the genomics of hMPXV indicates an ongoing evolutionary process that is influenced by selective pressures exerted by host species. One hypothesis suggests that the gradual loss of genes, particularly at the genome's terminal ends, plays a significant role in driving the evolution of these viruses (24), as well as recombination, genome size variation, and the involvement of the APOBEC3 enzyme. Of these, the last of the proposed factors represents the most viable alternative, although the evolution of hMPXV could be the result of the combination of all of them, thus explaining hMPXV's high capacity and great success in infecting a wide variety of hosts.

Vaccination against smallpox provides cross-protection against other *orthopoxvirus* (OPV) species, including monkeypox virus (MPXV). According to available data, about 90% of identified MPXV cases were in individuals who had not been infected with or vaccinated against smallpox, and individuals who had been previously vaccinated against smallpox showed 85% protection against MPXV (47). While several compounds have shown promise as antiviral therapies, vaccines remain the most effective means of controlling this virus and many other infectious diseases.

Indeed, the importance of vaccination is supported by the findings of Nguyen et al. (48), who estimated that in 2016, the year before the outbreak began in Nigeria, only 10.1% of the population was vaccinated, and population immunity, which takes into account declining immunity at the individual level, was a disturbing 2.6%, down from 65.6% in 1970. By 2018, the vaccinated population had declined to 9.3%, and estimated population immunity had declined to 2.2%. In our review of the literature, we found that unvaccinated individuals accounted for approximately 80% to 96% of the cases of MPXV (36).

Potentially catastrophic is the widespread consequences of the re-appearance of MPXV strains exhibiting significant human adaptability. Because there is a risk of establishing new reservoirs beyond Africa, the importation of MPXV by infected vertebrates is worrisome. Notably, American ground squirrels have shown susceptibility to infection, adding to the concern, as said susceptibility indicates the likelihood that other rodent species around the world may be similarly vulnerable (49). For this reason, genomic surveillance is essential, not only for the epidemiological recording and monitoring of the genetic divergence of the virus in humans but also to do the same in animals, which could become natural reservoirs of the disease in many parts of the world, thus complicating the containment of the virus.

Conclusions

After the global cessation of antipoxviral immunization following the eradication of MPXV, it is possible that said virus re-emerged to occupy the ecological niche left by the (similar) elimination of the smallpox virus. Factors such as urbanization, hunting, increased wildlife trade and heavy rainfall (especially when leading to flooding) may also contribute to humans approaching infected animals. The specific enrichment of APOBEC3 motif mutations in MPXV clade IIb since 2017 may explain the epidemiological shift that has occurred in recent years. Such a pattern could be caused by sustained transmission in a new host or a new route of infection. The MSM population was the main population affected by the 2022 outbreak, suggesting that sexual transmission routes and immune status are of interest in this new hMPXV clade.

Resumen

Objetivo: La viruela del simio es una enfermedad zoonótica viral endémica de África Central y Occidental, que se ha notificado en más países durante la última década en comparación con los 40 años anteriores. En 2022 se produjo un brote multinacional. Este cambio en la epidemiología del virus puede representar una adaptación evolutiva. Analizar los aspectos moleculares de la enfermedad por MPXV, por sus siglas en inglés, que puedan explicar su cambio de epidemiología durante el brote de 2022. Métodos: Se realizó una revisión narrativa desde el inicio del brote multinacional de MPXV en julio de 2022 hasta diciembre de 2022 de un total de 271 artículos publicados en las bases de datos *MEDLINE/PubMed* y *LILACS*, que se organizaron mediante el gestor de búsquedas y referencias *Mendeley Desktop* 1.19.4, se eliminaron los duplicados y que no se ajustaban al objetivo del estudio, seleccionando 49 artículos para la presente revisión. Discusión: El resurgimiento del MPXV plantea desafíos debido al declive de la inmunidad y los patrones epidemiológicos cambiantes. Los brotes recientes muestran diferentes vías de transmisión que afectan a nuevas demografías. La evolución genómica, el historial de vacunación y los posibles nuevos reservorios animales complican los esfuerzos de contención. La vigilancia continua y la vacunación son cruciales para el control. Conclusiones: Es posible que MPXV puede haber surgido para ocupar el nicho ecológico dejado por el virus de la viruela. Las mutaciones del motivo de la subunidad catalítica 3G de la apolipoproteína B en los virus del clado IIb de MPXV pueden explicar el cambio epidemiológico ocurrido en los últimos años. Este patrón podría deberse a una transmisión sostenida en un nuevo huésped o a una nueva vía de infección.

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