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MAJOR ARTICLE

Exportation of Monkeypox Virus From the African Continent

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Background. The largest West African monkeypox outbreak began September 2017, in Nigeria. Four individuals traveling from Nigeria to the United Kingdom (n = 2), Israel (n = 1), and Singapore (n = 1) became the first human monkeypox cases exported from Africa, and a related nosocomial transmission event in the United Kingdom became the first confirmed human-to-human monkeypox transmission event outside of Africa.

Methods. Epidemiological and molecular data for exported and Nigerian cases were analyzed jointly to better understand the exportations in the temporal and geographic context of the outbreak.

Results. Isolates from all travelers and a Bayelsa case shared a most recent common ancestor and traveled to Bayelsa, Delta, or Rivers states. Genetic variation for this cluster was lower than would be expected from a random sampling of genomes from this outbreak, but data did not support direct links between travelers.

Conclusions. Monophyly of exportation cases and the Bayelsa sample, along with the intermediate levels of genetic variation, suggest a small pool of related isolates is the likely source for the exported infections. This may be the result of the level of genetic variation present in monkeypox isolates circulating within the contiguous region of Bayelsa, Delta, and Rivers states, or another more restricted, yet unidentified source pool.

Keywords. monkeypox virus; viral genomes; exportation; travel epidemiology; border health; haplotype networks.

Monkeypox virus (MPXV) is a species of large double-stranded DNA viruses belonging to the genus *Orthopoxvirus*. It is the etiological agent of the zoonotic disease monkeypox (MPX), which was first identified as a human pathogen in the Democratic Republic of the Congo (DRC, formerly Zaire) in 1970 [1]. In the nearly 50 years since, human cases of MPX have been identified in 11 African countries and MPXV is considered endemic in the DRC [2]. Based on serological data, MPXV is evidenced to be maintained by various mammalian species in endemic areas [3], with periodic introductions into human populations, where relatively short chains (≤7) of human-to-human transmission can occur [4–6]. Genetically, there are 2 clades of MPXV [7]. The West African clade is known to occur from western Cameroon to Sierra Leone, whereas the Congo Basin clade has been detected from central and southern Cameroon to the DRC [8, 9]. Potential routes of exposure include interaction with wild animals and close proximity to sick individuals, as well as contact with infectious fomites [10, 11].

The largest West African MPX outbreak in history began in Nigeria in September 2017 [12]. No exported cases were reported for the first 11.5 months of the outbreak; however, within a 3-week period from 2 to 23 September 2018, 3 unlinked travelers infected with MPXV left Nigeria and arrived in 2 countries [13, 14]. Seven months later, a Nigerian national became ill with MPX in Singapore [15]. These exportations represent the first time a human host was documented to transfer MPXV from the African continent; however, there are a handful of examples of MPX outbreaks in animals within laboratories and zoos with no clearly identified source of infection since it was first identified in 1958 [16–18]. The source of the 2003 United

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States (US) MPX outbreak was determined to be a shipment of rodents from West Africa [19].

The goal of this study was to better understand the relationship of exported cases in the context of the outbreak. A multidisciplinary approach was established to identify geographic and temporal trends, as well as possible links between cases to elucidate factors that might have contributed to the exportation of human MPX cases from Africa. To achieve this goal, we defined the following objectives: (1) to generate full genome sequences from viral isolates obtained from outbreak cases within Nigeria as well as exported cases; (2) to use genomic analyses to hypothesize relationships of exported cases to one another and to other viruses from the outbreak; (3) to evaluate the exported variants temporally and spatially in the context of the broader outbreak; and (4) to use these data to derive inferences regarding commonalities.

MATERIALS AND METHODS

Diagnosis, DNA Sequencing, and Genome Assembly

Table 1 presents demographic and epidemiological data for Nigerian nationals who traveled to the United Kingdom (UK1 and UK2) and Singapore (SING), as well as an Israeli national who returned to Israel (ISR) after living in Nigeria, and a UK healthcare worker (UK3) who was exposed to UK2 [20]. Methods of diagnostic confirmation for these cases were reported previously [13–15, 20], and those of Nigerian cases herein followed methods outlined previously [12].

For this study, genomic data were generated for 10 MPXV isolates, including the 4 exported cases (UK1, UK2, ISR, SING); 1 nosocomial transmission case within the UK (UK3); and 5 Nigerian MPX outbreak cases. Nigerian cases were selected based on geographic location and sample availability/quality. Samples were included from all states the exported cases reported visiting up to 3 weeks prior to symptom onset, except for Ebonyi State (visited by SING) where no cases have been confirmed [21]. Additionally, 1 case from Bayelsa State (BAY) was included, as Bayelsa is adjacent to both Delta and Rivers states (visited by export cases). To increase representation of genomes from known epidemiologically linked clusters, 3 previously generated but unpublished genomes from the 2003 US outbreak were included [7]. Case confirmation, sequence data generation, and genome assembly methods for the Nigerian and Singapore samples followed those outlined previously [12, 22]. GATU was used for sequence annotation [23]. For UK1, UK2, and UK3, pustule swab samples were processed for genomic sequencing. Sequencing was conducted on the Illumina MiSeq platform using the Nextera XT sequencing kit according to the manufacturer's instructions. Reads were automatically trimmed using Trimmomatic [24] to an average phred score of Q30 across the read. To acquire additional genomic coverage, libraries were prepared and sequenced on the MinION platform (Oxford Nanopore Technologies) from the same samples. Viral

Table 1. Epidemiological Data for Exportation-Related Cases

Case	Age, y	Nationality	Sex	Date of Symptom Onset	Departure From Nigeria	Nigerian States Visited[a]	Reported Exposure Risks
UK1	32	Nigerian	M	1 Sep 2018	2 Sep 2018	Rivers (1–19 Aug), Delta (19–28 Aug), FCT (28 Aug–2 Sep)	None
UK2	36	Nigerian	M	1 Sep 2018	4 Sep 2018	Lagos, Delta, Lagos (dates unknown)	Consumption of bushmeat and contact with sick individual with an MPXV-like rash
UK3	40	British	F	22 Sep 2018	N/A	N/A	HCW who had contact with UK2 on 6–10 Sep 2018
ISR	38	Israeli	M	29 Sep 2018	23 Sep 2018	Rivers	Disposed of 2 rodent carcasses (in Rivers State) on 17 Sep 2018
SING	38	Nigerian	M	30 Apr 2019	28 Apr 2018	Delta (1–21 and 23–28 Apr), Ebonyi (21–23 Apr)	Reported potentially eating bushmeat at a wedding in Ebonyi State
BAY	30	Nigerian	M	14 Aug 2018	N/A	Bayelsa	Occupational (HCW)

Abbreviations: BAY, Bayelsa State; F, female; FCT, Federal Capital Territory; HCW, healthcare worker; ISR, Israel; M, male; MPXV, *Monkeypox virus*; N/A, not applicable; SING, Singapore; UK, United Kingdom.

[a]States visited in the 3 weeks prior to departure from Nigeria.

isolation and tissue culture was conducted for samples of UK2 and UK3. The UK2 tissue culture sample was sequenced using the MinION platform and the UK3 tissue culture sample was sequenced on the MiSeq platform. Direct comparison between raw data of primary and tissue culture samples for UK3 were compared and revealed no differences. Therefore, sequence data from both direct sequencing of lesion swabs and tissue culture samples were utilized to generate a full genome for the viral genome of UK3. De novo assembly was conducted for UK1 and UK3 using the CLC Genomic Workbench 12.0 (Qiagen, Aarhus, Denmark), whereas the UK2 direct sample sequenced reads were mapped to a de novo assembled genome generated from UK2 tissue culture sequence data using Map Read to Reference in the CLC. Genome sequencing and assembly for the Israel sample was reported previously [25]. Additional details are available in the Supplementary Data.

Genetic Analyses

The 10 newly generated sequences were aligned with 5 sequences from the 2003 US outbreak (3 previously unpublished) [7], as well as 7 previously published genomes from Rivers State [12] (visited by 2 exportation cases), and 2 published historic Nigerian genomes [8]. Two epidemiologically linked clusters are represented within the reference samples (Table 2) to provide baseline data regarding expected genetic variation present within a cluster of epidemiologically linked cases. Only sequences containing <1% ambiguous bases were selected given the sensitivity of haplotype analyses to missing data. Sequences were aligned using MAFFT version 7.215 [26] with the ns-i algorithm and maximum iterations = 15. The full-length alignment with gaps removed (183667 nt) was visually inspected using Geneious version 11.1.2 (BioMatters, Auckland, New Zealand). Phylogenetic inference was conducted using the MPI version of MrBayes version 3.2.2 [27] to generate a majority rules consensus tree with the following parameters: ngen = 20 000 000, samplefreq = 2000, nruns = 2, nchains = 4, nst = 6. A single-nucleotide polymorphism (SNP) matrix 491 nt in length, generated from the full-length alignment (excluding columns with gaps, ambiguous bases, or invariable sites) was analyzed using the median joining algorithm in PopART [28] to generate a haplotype network. SNPs were quantified using Geneious.

For reference, 23 previously published MPXV genomes (GenBank accession numbers JX878407–JX878429) [29] from Sankuru Health District in DRC were utilized to generate a SNP matrix as detailed above. Epidemiological data (date and health zone) were included for examination of geographic and genetic variation. Mutational differences for all SNP matrices were calculated using Geneious.

RESULTS

Exportation of 3 MPX cases (UK1, UK2, and ISR) from Nigeria occurred over a 3-week period between 2 and 23 September 2018, approximately 11 months after the peak of the epidemic (October 2017) [12]. A healthcare worker (UK3), who was exposed to UK2, became symptomatic on 22 September 2018, and a fourth exportation (SING) occurred 28 April 2019, >7 months after the initial exportation. Except for the documented relationship between UK2 and UK3, questionnaires, timelines, and travel histories did not reveal an epidemiological link between the travelers (Table 1 and Figure 1). No city or state was visited by all international travelers, although all exportation cases individually visited either Delta State or Rivers State, which share a border (Figure 2).

Phylogenetic analyses confirmed monophyly for all Nigerian samples within the West African clade of MPXV (Bayesian posterior probability [BPP] = 1) as previously reported [12]. Additionally, Bayesian inference determined that all exported cases (UK1, UK2, UK3, SING, ISR) shared a most recent common ancestor (MRCA; Figure 3) with a single case from Bayelsa State. The BAY sample was obtained on 14 August 2018, from a MPXV-positive healthcare worker employed at the Niger Delta University Teaching Hospital,

Table 2. Genomes Included in Analyses

Case	GenBank Accession No.	Locality Identified	Reference
UK1	MT903343	Cornwall, UK	This study
UK2	MT903344	Blackpool, UK	This study
UK3	MT903345	Blackpool, UK	This study
SING	MT903342	Singapore	This study
ISR	MN648051	Israel	[25]
BAY (M5320)	MT903341	Bayelsa State, Nigeria	This study
M5312	MT903340	Rivers State, Nigeria	This study
M2957	MT903338	Lagos State, Nigeria	This study
M2940	MT903337	FCT, Nigeria	This study
M3021	MT903339	Delta State, Nigeria	This study
M2920	MK783033	Rivers State, Nigeria	[12]
M3025	MK783030	Rivers State, Nigeria	[12]
M3018[a]	MK783027	Rivers State, Nigeria	[12]
M3019[a]	MK783028	Rivers State, Nigeria	[12]
M3029[a]	MK783029	Rivers State, Nigeria	[12]
M3020[a]	MK783031	Rivers State, Nigeria	[12]
M3030	MK783032	Rivers State, Nigeria	[12]
Nigeria 1971	KJ642617	Abia State, Nigeria	[8]
Nigeria 1978	KJ642615	Oyo State, Nigeria	[8]
USA2003_039_Hu[b]	DQ011157	Wisconsin, US	[7]
USA2003_044_PD[b]	DQ011153	Wisconsin, US	[7]
USA2003_099_GR[b]	MT903346	Wisconsin, US	This study/ [7][c]
USA2003_206_DM[b]	MT903347	Illinois, US	This study/ [7][c]
USA2003_233_RS[b]	MT903348	Illinois, US	This study/ [7][c]

Abbreviations: BAY, Bayelsa State; FCT, Federal Capital Territory; ISR, Israel; SING, Singapore; UK, United Kingdom; US, United States.

[a]Linked cases from the Port Harcourt prison in Rivers State.

[b]Linked cases from the 2003 US outbreak: DM, dormouse; Hu, human; GR, Gambian pouched rat; PD, prairie dog; RS, rope squirrel.

[c]Sequences generated previously but first published herein.

north of Yenagoa, Bayelsa State. Bayesian inference was unable to provide resolution of relationships within this group of samples, other than high statistical support (BPP = 1) for a sister relationship between UK2 and UK3 samples. Two clusters of cases with known epidemiological links (the 2003 US outbreak and the Port Harcourt prison cluster) were also determined to be monophyletic with high statistical support (Figure 3).

Haplotype analyses similarly grouped the same 6 isolates (UK1, UK2, UK3, SING, ISR, and BAY; red highlighted box of Figure 4), further supporting that the exported cases and BAY (collectively referred to as exportation-related cases) share an MRCA. Similar grouping was seen with the US outbreak and Port Harcourt prison samples clustering together, respectively. Pairwise genetic distance calculations (Table 3) indicate that clusters of epidemiologically linked cases in the US outbreak and Port Harcourt prison had averages of 0.4 and 1.5 SNPs between genomes, respectively. The exportation-related cases studied herein (including BAY) had an average of 5.9 SNPs between sampled genomes, whereas unrelated cases across Rivers State (excluding the prison cluster and exportation-related samples) averaged 21.0 SNPs between genomes.

The haplotype analysis of the genomes from Nigeria also revealed that samples from different Nigerian states, occurring months apart, were separated by as few as 3 SNPs (M5312 from Rivers vs M2957 from Lagos; Figure 4). Examination of the Sankuru Health District dataset identified multiple examples of genomes from the same health zone separated by <5 SNPs, as well as samples differing by 5–9 SNPs (similar to the exportation-related cases) occurring across different health zones and years.

DISCUSSION

Genetic and Epidemiological Investigation of Cases

Only a handful of MPX outbreaks involving animals within zoos or primate colonies in Europe and the US have been documented, with uncertain/unconfirmed origin of the disease [16, 17]; however, human cases of MPX outside Africa are even less common. Despite thousands of MPX cases across Africa since 1971, these were the first human MPX cases outside of Africa since the 2003 US outbreak, which was caused by imported African rodents [19]. Furthermore, they were the first documented infected humans to leave Africa, and all occurred within a period of 9 months. For these reasons, an in-depth investigation into these cases was conducted.

The combined examination of genetic and epidemiologic data indicate no direct link between the exportation-related cases, with the exception of the UK2 and UK3 nosocomial transmission, which is supported by lack of mutational differences, high statistical support of phylogenetic relationships, and identified epidemiological link. The identified genetic variation within the exportation-related cases is higher than clusters of epidemiologically linked cases (ie, US outbreak

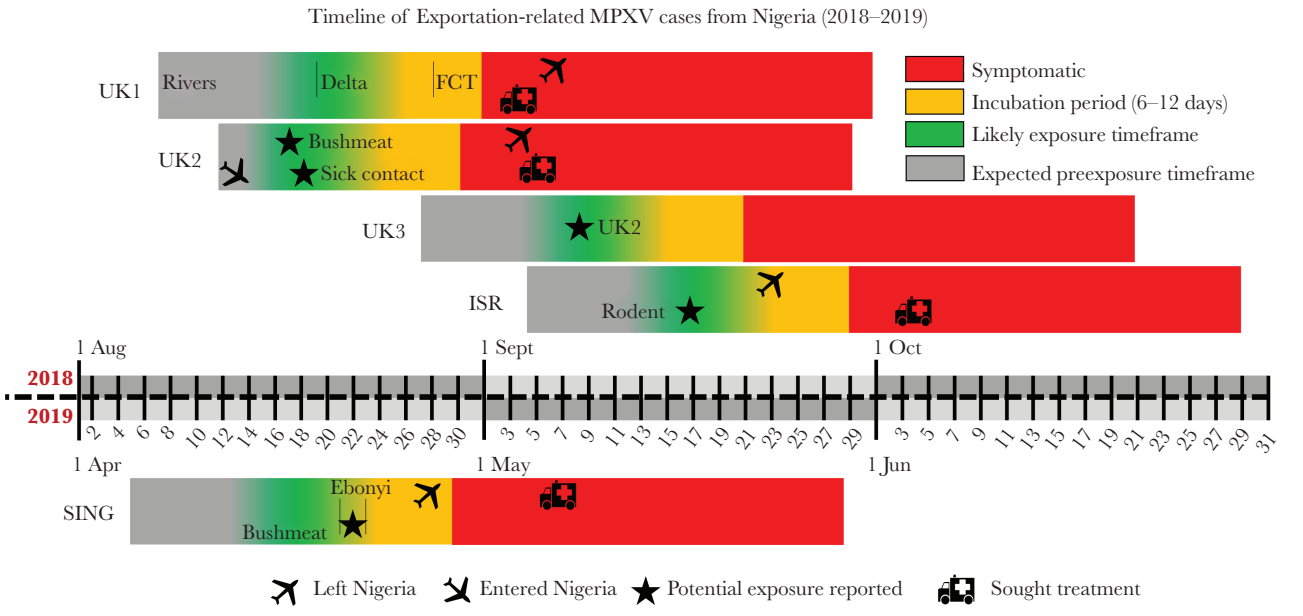

Figure 1. Timeline figure of *Monkeypox virus* cases exported from Nigeria in fall (August–October) of 2018 and spring (April–June) of 2019, shown above and below the timeline, respectively. Delineations between exposure time frame and incubation timeline are gradated, as variations are known to occur. Dates of travel between states are not known for UK2. Vertical black lines within the timeline for UK1 and SING indicate travel between states and/or the Federal Capital Territory. Symptom onset is based on cases reporting presence of lesions or fever prodrome. Incubation time is documented to range typically from 6 to 12 days, with an upper bound of 16 days. These numbers were used to determine likely timelines for exposure (green), as well as timeline expected to be prior to exposure (gray). Abbreviations: FCT, Federal Capital Territory; ISR, Israel; MPXV, *Monkeypox virus*; SING, Singapore; UK, United Kingdom.

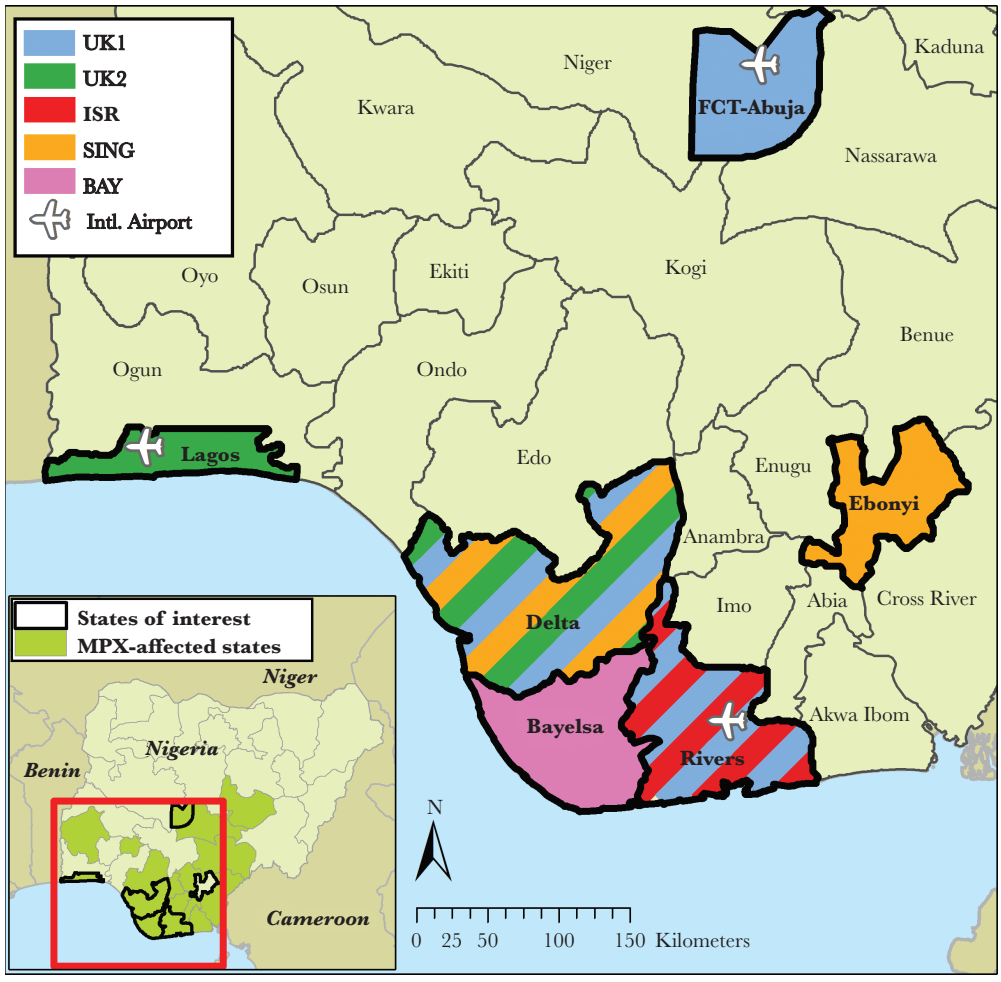

Figure 2. Map of southern Nigeria, indicating states visited by cases within the exportation-related group (states of interest). Shading within the map indicate states visited by individual travelers. Green-shaded states within the inset map indicate states with confirmed monkeypox cases as of April 2019. Abbreviations: BAY, Bayelsa State; FCT, Federal Capital Territory; ISR, Israel; MPX, monkeypox; SING, Singapore; UK, United Kingdom.

and Port Harcourt prison clusters), which, along with the epidemiological data, suggests no direct link between cases. Furthermore, the level of genetic differentiation among these samples is lower than the average number of SNPs seen across all outbreak samples (Table 3), suggesting the possibility that these viral genomes are not truly independent samples. Last, this intermediate amount of genetic variation is comparable to that of a number of unrelated MPXV genomes obtained within a defined geographic region (ie, Sankuru District in DRC), implying that this quantity of SNPs could be explained by population-level genetic variation. Based on these data and travel history, it could be hypothesized that exportation-related and BAY viral isolates were contracted within the contiguous region of Rivers State, Delta State, and Bayelsa State. This framework lends itself to 2 independent hypotheses: (1) a single unidentified source, or small source pool, is responsible for infection of these individuals, or (2) these cases have no causal link and this level of genetic relatedness is due to genetic variation present within the area of study (ie, natural/random differentiation between viruses circulating in the animal community).

Among the genetic sequences available from areas of Nigeria where the 4 travelers visited in the 3 weeks prior to illness, both phylogenetic inference and haplotype analyses indicate that BAY is the most closely related Nigerian MPXV isolate (sequenced to date) to the exported cases and that these 6 sequences share an MRCA. The existence of an MRCA does not necessarily imply that these samples come from a single source during the timeframe of the outbreak, but that at some point in the past (recent or relatively distant), the exportation-related MPXV genomes shared an ancestor more recently than with any other genomes sequenced to date. It is unclear at what time this MRCA (black dot within red highlighted cluster in Figure 4) originally occurred, but given the temporal span of these cases, it appears this MRCA first occurred prior to August 2018, and its descendants continued to circulate until at least as recently as April 2019. Neither phylogenetic inference nor haplotype analyses could determine relationships among these

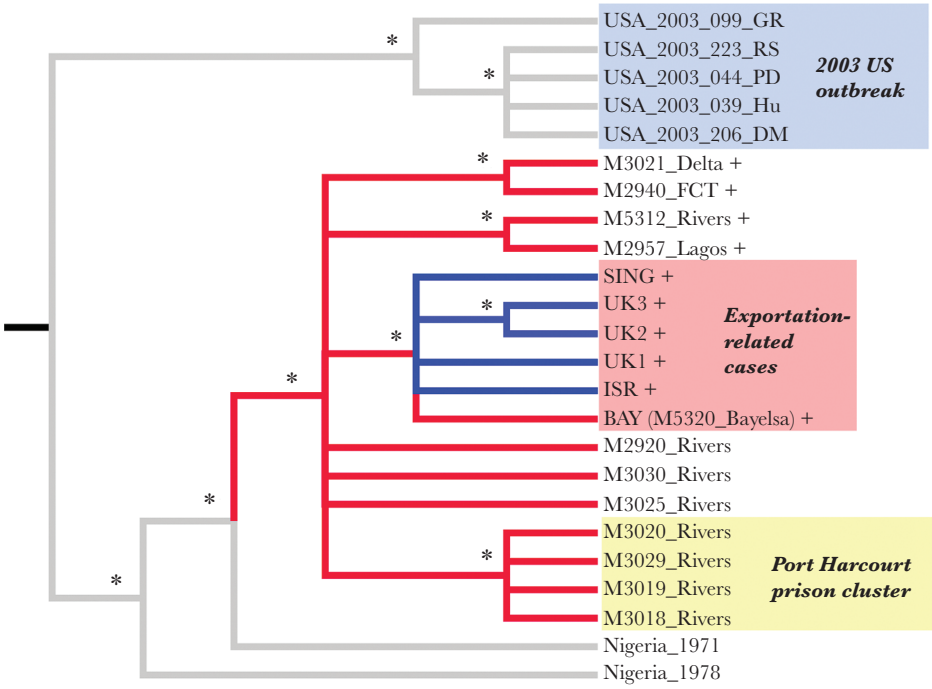

Figure 3. Bayesian inference phylogenetic cladogram. Branch lengths are not informative. Blue branches represent exported cases, red branches represent in-country outbreak cases, and gray branches indicate reference samples. *Relationships with Bayesian posterior probability values >99%. Samples from epidemiologically linked *Monkeypox virus* clusters (blue- and yellow-highlighted boxes) served as references for genetic variation and ability of Bayesian inference to group epidemiologically linked genomes with high statistical support. Exportation-related cases are highlighted in pink. [+]Sequences generated for this study. Abbreviations: BAY, Bayelsa State; DM, dormouse; FCT, Federal Capital Territory; GR, Gambian pouched rat; HU, human; ISR, Israel; PD, prairie dog; RS, rope squirrel; SING, Singapore; UK, United Kingdom; US, United States.

isolates, except consistently grouping UK2 and UK3 (the result of a documented human-to-human transmission event) together. Additionally, the contiguous region comprised of Rivers, Bayelsa, and Delta states was visited by all exportation-related cases (including BAY; Figure 2) within the 3 weeks prior to symptom onset, and is therefore the most parsimonious geographic area of exposure. Admittedly, given the movement of people and goods, the locality of exposure may or may not be where the virus circulates in wildlife.

The earliest case in this cluster (BAY) was isolated from a healthcare worker at a hospital, <50 km by road from major border crossings to either River State or Delta State. Considering the amount of interstate travel through this region, it is possible the BAY genome originated in either adjacent state (Figure 2). The lack of confirmed epidemiological links between cases, timeline data (Figure 1), and the increased level of genetic variation when compared to other epidemiologically linked clusters (eg, the 2003 US outbreak and the Port Harcourt prison cluster; Figure 4; Table 3) suggest no direct links between the exportation-related cases, with the exception of UK2 and UK3.

Both the Sankuru [29] and Nigerian datasets illustrated that highly similar MPXV strains can circulate across years within the same area, indicating that genetic similarity alone cannot identify human-to-human transmission. At the same time, relatively divergent strains have been detected within the same area [12] (Figure 2), suggesting complexity within fine-scale phylogeographic patterns. The fact that more geographically disparate samples can share an MRCA than samples from the same village could be caused, at least in part, by movement of humans and animals. Sick humans, animals, and animal products can be transported between states or countries with relative ease, transporting viral genomes in the process, further complicating fine-scale analysis of pathogen genetic variation. For these reasons, it is important to consider both epidemiological and genetic data when investigating MPX transmission events.

Given that the average number of SNPs between genomes in the exportation-related clade is lower than the average number of SNPs observed among other outbreak strains as a whole, it is possible that all or some of these individuals involved in the exportation events were exposed to the same source, or to a limited number of unidentified sources sharing an MRCA. Examples of potential sources, which might be difficult to identify with standard case questionnaires, include an unidentified ill mutual acquaintance, exposure to a group of infected animals (eg, pets, livestock, household pests, or wildlife), meat, or animal products at a market or street vendor. Few parts of wild animals go to waste, with some being sold as bushmeat, others being utilized for traditional medicine, and still others used in religious ceremonies, which have all been documented in Nigeria [30–32].

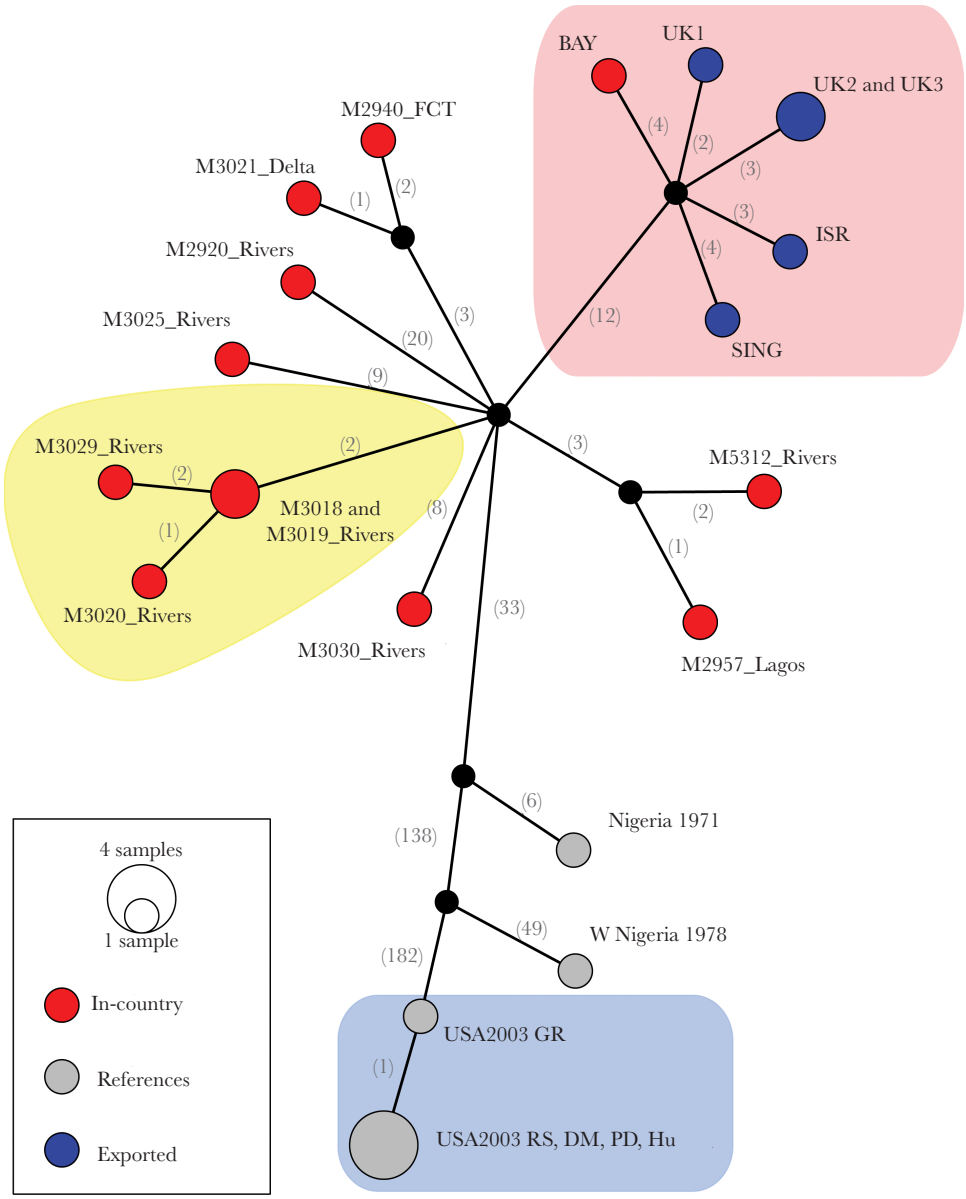

Figure 4. Median-joining haplotype network depicting relationships between *Monkeypox virus* samples based on single-nucleotide polymorphism matrix from whole genome data. Yellow-highlighted area indicates a cluster of epidemiologically related cases from Port Harcourt prison discussed previously [12], blue-highlighted samples represent epidemiologically linked cases from the 2003 United States outbreak generated from both human and animal samples, and pink-highlighted samples indicate the exportation-related cases, including the closest identified relative within Nigeria. Abbreviations: BAY, Bayelsa State; DM, dormouse; FCT, Federal Capital Territory; GR, Gambian pouched rat; Hu, human; ISR, Israel; PD, prairie dog; RS, rope squirrel; SING, Singapore; UK, United Kingdom; US, United States.

It is also possible human MPX cases involving viruses with this level of genetic variation resulted from independent primary transmission events from wildlife to humans. This possibility has been supported by similar genomes being identified in separate Nigerian states or health zones in Sankuru, DRC. Were the exported cases representative of a random sampling of MPXV genomes from those circulating across Nigeria, one would expect these genomes to be scattered throughout the phylogenetic tree or haplotype network. The monophyly of exportation-related cases seems to support the conclusion that a nonrandom sample of MPXV isolates was exported from

Table 3. Average Genetic Distance (Number of Single-Nucleotide Polymorphisms) Between Samples for Each Defined Group

Samples Compared	No.	Average SNPs[a]
2003 US outbreak	5	.4
Port Harcourt prison cluster	4	1.5
Exportation-related	6	5.9
All Rivers State samples	8	12.4
Nonprison Rivers State samples	4	21.0
All Nigerian outbreak samples	17	15.5

Abbreviation: SNP, single-nucleotide polymorphism.

[a]SNPs (point mutations) present across the whole genome alignment for the dataset examined.

Nigeria. This would support the hypothesis that an unknown link or commonality (eg, social behavior, common destination, common population of viral genomes) exists between these cases.

Timing and Quantity of Exportations

Given the prevalence of international travel, exportation of human MPX cases from Africa may have been considered a high likelihood. Despite this, there are several items which, when viewed together, raise intriguing questions. First, these exportations occurred well after the peak of the epidemic in 2017. During the first 12 months of the outbreak, 115 confirmed cases were reported, including confirmed cases in Enugu State, Lagos State, Rivers State, and the Federal Capital Territory, which contain 4 of the 5 international airports with continual operation in Nigeria. Despite the number of confirmed and suspected cases in proximity to large airports, no known cases were exported during the first 11.5 months of the outbreak. Second, 3 epidemiologically unrelated persons (all males) left the country during a 3-week period, all having been exposed to MPXV prior to departure. Third, the MPXV genomes from all exported cases spanning 8 months share a common ancestor, suggesting a lack of random sampling of exported MPXV genomes.

If risk of exportation was dependent on disease incidence rate (ie, frequency), we would have expected exportation events to occur near the peak of the epidemic. If risk was constant across time, one might expect exportations to occur relatively evenly spaced. Neither of these explanations accounts for the clustering of 3 exported cases nearly a year after the peak of the epidemic, suggesting instead some sort of precipitating event or variable. Seasonal differences in rainfall and other ecological factors have been documented to impact behavior of bushmeat species and hunters in Nigeria [33, 34]. The seasonal variation of animal/hunter behavior and bushmeat availability in Nigeria could impact frequency of interactions and disease transmission between certain species and humans. If strict seasonality was responsible, it is difficult to explain why there were no exported cases reported in September–October 2017, during the peak of the outbreak.

With no clear MPXV source pool identified to account for the exported disease, it is possible some characteristic of the outbreak changed. Perhaps the prevalence of MPX cases shifted to a more urban distribution over the course of the outbreak, where international travelers are more abundant. It may be that 1 or 2 independent events increased exposure risk to this population of travelers—for example, a scenario whereby MPXV-infected animals and/or animal products from a small geographic area appeared intermittently in 1 or more urban markets more likely to be frequented by international travelers.

The varying level of epidemiological data available from each case and the relatively small number of full genome sequences generated when compared to the overall outbreak number have limited the level of resolution at this time. With these limitations considered, the contiguous region containing Delta, Rivers, and Bayelsa states was visited by all cases, which formed the exportation-related clade. These cases share an ancestor with each other more recently than other sequenced genomes from the outbreak, although neither epidemiological data nor the average number of SNPs between these genomes support the hypothesis of human-to-human transmission. The clustered timing of exportations has not yet been explained, but may be the result of a change in some aspect of the overall outbreak, a recurring event, seasonality, or random chance.

In December 2019, Public Health England confirmed an additional case of MPXV in an individual with recent travel to Nigeria. No genetic data are currently available for inclusion in this study. The continued exportation of human MPX cases from Nigeria is concerning. When analyzed together, detailed molecular and epidemiological data can provide a clearer picture of disease dissemination. Unfortunately, in outbreak scenarios, these data are not always consistently collected, leaving gaps in datasets and interpretations.

Outbreak responses are often complex, with new cases appearing in clusters and frequently overwhelming limited resources of rural or regional health centers. The dissemination of information and start of centralized official case investigations may be delayed, resulting in loss of genetic and epidemiologic data. For these reasons, detailed training and subsequent refreshers of frontline healthcare workers in methods of collecting and cataloging detailed and consistent information/biological samples from cases can greatly increase the amount of information available for examination. To address these issues, Nigeria implemented the Surveillance, Outbreak Response Management and Analysis System (SORMAS) across portions of 8 states in November 2017 for the monkeypox outbreak [35]. Implementation of SORMAS not only increased communication of aggregate case data, but also increased the quantity of epidemiological data collected. Permanent implementation of this type of system over a broader geographic range with increased training can drastically improve the quality and quantity of epidemiological data collected in domestic and international settings.

In this age of increasing travel, it is important to remember that political borders have no impact on movement of pathogens. As international travel continues to increase, using travelers as sentinels or an indicator of sorts has the ability to detect changes in patterns and prevalence of disease occurrence that may otherwise have gone unnoticed [36, 37].

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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