 doi:10.20944/preprints202208.0128.v1

Review

Atypical and Unique Transmission of Monkeypox Virus during the 2022 Outbreak: An Overview of the Current State of Knowledge

Jade C. Riopelle [1], Vincent J. Munster [1,*], and Julia R. Port [1,*]

[1] Laboratory of Virology, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Hamilton, MT, USA
* Correspondence: JRP – julia.port@nih.gov; VJM – vincent.munster@nih.gov

Abstract: An ongoing monkeypox outbreak in non-endemic countries has resulted in the declaration of a Public Health Emergency of International Concern by the World Health Organization (WHO). Though monkeypox has long been endemic in regions of Sub-Saharan Africa, relatively little is known about its ecology, epidemiology, and transmission. Here, we consider the relevant research on both monkeypox and smallpox, a close relative, to make inferences about the current outbreak. Undetected circulation, combined with atypical transmission and case presentation, including mild and asymptomatic disease, have led to the spread of monkeypox in non-endemic regions. Broader availability of diagnostics, enhanced surveillance, and targeted education, combined with a better understanding of the routes of transmission, are critical to identify at-risk populations and design science-based countermeasures to control the current outbreak.

Keywords: monkeypox; transmission; outbreak; atypical presentation

1. Introduction

In May 2022, a case of monkeypox (MPX) was initially reported in the United Kingdom. As of August 1, 2022, this outbreak includes over 22,485 confirmed MPX cases across 72 countries (**Figure 1A**) and is considered a Public Health Emergency of International Concern by WHO. Uniquely, the current outbreak appears able to sustain efficient human-to-human monkeypox virus (MPXV) transmission, in contrast to historical MPX outbreaks in both Central and West Africa (1). All affected countries classify as non-endemic (**Figure 1A**), and many have never experienced MPX cases before (2).

MPXV is a DNA virus in the *orthopoxvirus* (OPXV) genus, which includes smallpox virus, which has been eradicated through vaccination campaigns (3). MPXV was first discovered in an outbreak in non-human primates (NHPs) in a Danish lab in 1958 (4). Human infection was documented for the first time in 1970 in the Democratic Republic of the Congo (DRC)(5). MPX is endemic to several West and Central African countries (6) (**Figure 1B**).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 8 August 2022 doi:10.20944/preprints202208.0128.v1

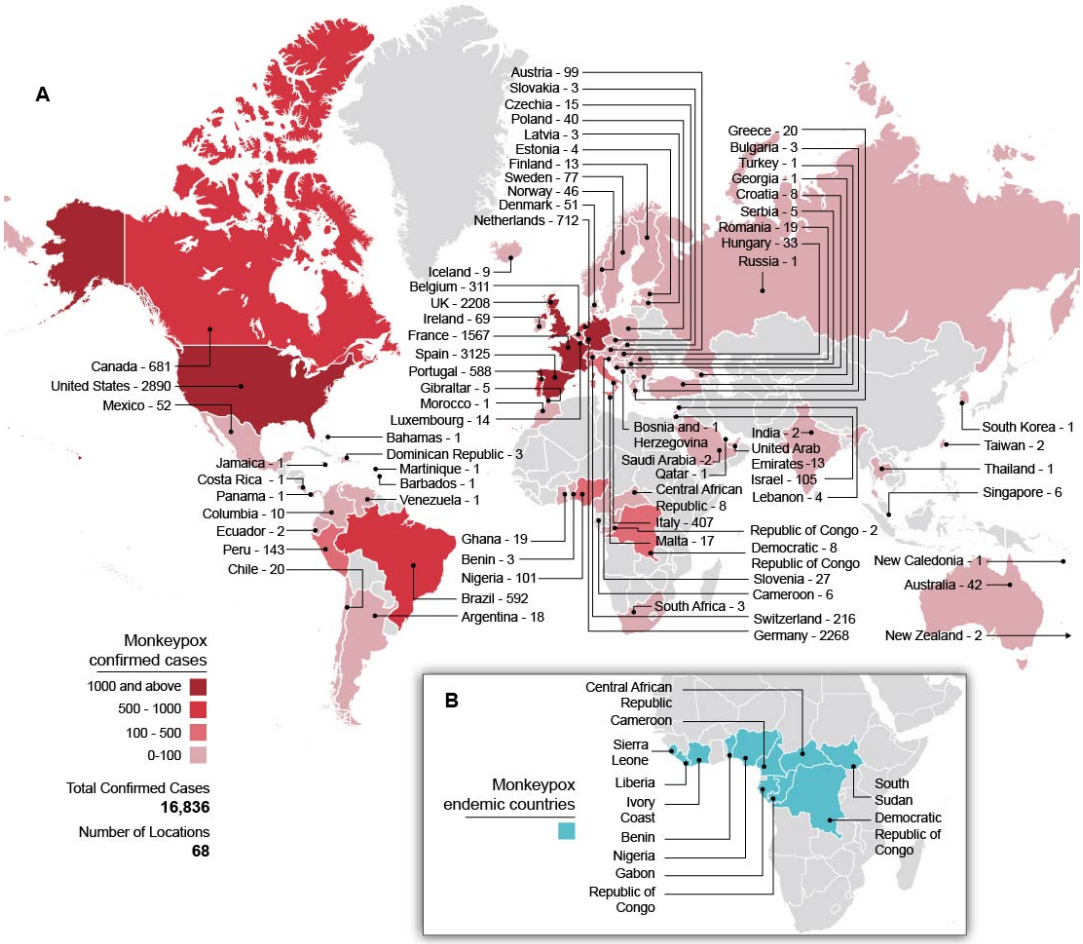

Figure 1. Global distribution of MPX cases. (**a**) MPX cases per country described in the current outbreak through July 27, 2022, as well as total confirmed cases and affected countries. Countries colored according to case count. Gray shading indicates no known cases. (**b**) Countries historically endemic for MPXV. Gray shading indicates non-endemic countries.

There are two phylogenetically distinct lineages of MPXV, which were named the Central African (CA) and West African (WA) clades. These lineages are analogous to the two strains of smallpox, *Variola major* and *minor*. Updated nomenclature lists the former CA clade as Clade 1, while Clades 2 and 3 correspond to the WA clade (7). In humans, MPX presents with a 2–4-day prodrome followed by appearance of a rash (8), though Clade 1 MPXV has increased morbidity, mortality, viremia, and transmissibility (9). Case fatality rates (CFRs) across previously reported outbreaks have averaged 3·6% for Clade 1 MPXV and 10·6% for Clades 2 and 3 MPXV (5).

Historically, it has been thought that MPXV and smallpox are only transmissible after the appearance of the rash and that subclinical infections are rare. However, documentation of potentially asymptomatic MPXV infections (10, 11) challenges this. In fact, in the current outbreak, many patients are presenting without a prodromal phase and with mild or asymptomatic disease. The sustained human-to-human transmission seen in the current outbreak has not been previously observed and highlights the need for more information about the spread of MPXV. A full understanding of MPXV transmission

 doi:10.20944/preprints202208.0128.v1

requires an understanding of its ecology and spillover alongside determinants of human-to-human transmission.

2. Ecology

Based on the presence of MPXV and OPXV antibodies, MPXV is thought to have a range of potentially suitable hosts, encompassing a wide variety of rodents and primates as dead-end hosts (12-17). Though MPXV is the only known OPXV circulating in West and Central Africa, the possible presence of other OPXVs hampers definitive measurements of true MPXV prevalence. MPXV has only been successfully isolated from a dead sooty mangabey (18), a symptomatic rope squirrel (19), and the feces of a symptomatic chimpanzee (20). There has been no documentation of reverse spillover events (21) or outbreaks in domestic animals. However, detection of OPXV antibodies in domestic pigs in DRC (17) and peridomestic rats in Uganda (22) underscores the zoonotic and cross-species potential of OPXVs.

The exact reservoir host complex remains unknown, though two major candidates have been posited: giant pouched rats (*Cricetomys gambianus,* detection of OPXV antibodies) and rope squirrels (*Funisciurus* spp., detection of OPXV antibodies and virus isolation)(4, 19) (13, 17, 23). Ecological niche models (ENMs) find rope squirrel, but not giant pouched rat, presence to be a significant predictor of MPXV geographical range (24, 25). Epidemiological studies have confirmed that human cases are in fact higher in areas predicted by ENMs to be ecologically suitable (26, 27). In DRC, an increased prevalence of MPXV-specific antibodies was found in humans living in forested areas as opposed to the savannah (28).

3. Spillover

Outbreaks of MPX generally start with a spillover event followed by limited human-to-human transmission (**Figure 2A**). Many potential routes of zoonotic transmission have been posited. In endemic areas, direct contact with animals, including dead or sick animals (8, 29), as well as hunting, butchering, and eating bushmeat (12, 30-34), have been linked to infection. Bites and scratches have also been implicated (35), as has indirect transmission (i.e., via respiratory droplets). Highlighting the difficulties in elucidating potential routes of spillover are reports available from a 2003 outbreak in the USA. An individual fell ill after a symptomatic prairie dog had been in their home without purportedly touching any surface in the home and without having any interaction with the animal (11), though a different study found no association between being in the vicinity of a sick prairie dog and MPXV infection (35). Experimental studies demonstrating successful aerosol inoculation of primates (36), as well as transmission studies in rope squirrels (14) and baboons (37), highlight different potential routes of spillover.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 8 August 2022 doi:10.20944/preprints202208.0128.v1

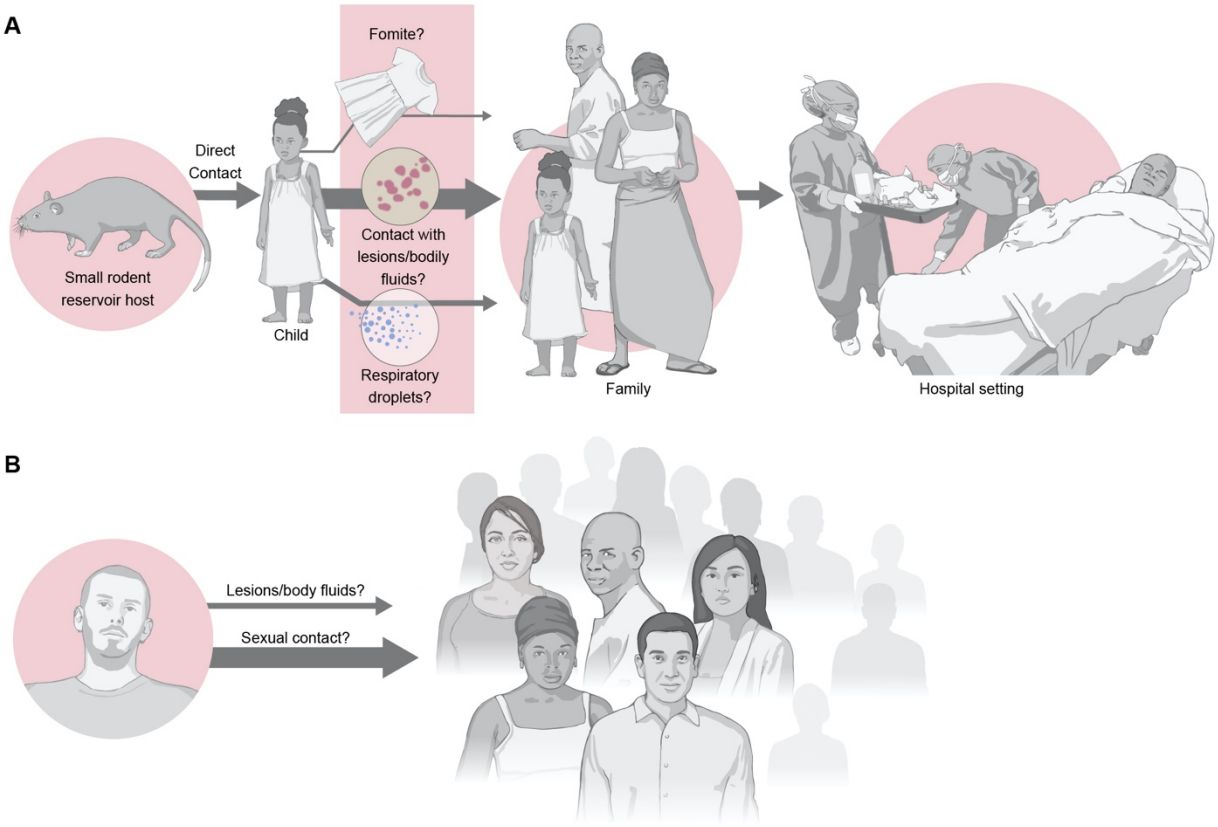

Figure 2. Posited routes of MPXV spillover and human-to-human transmission. (**a**) Proposed ecological spillover cycle for MPXV in endemic areas. (**b**) Proposed transmission routes in the current outbreak, with sexual contact transmission the most likely route for most transmission events. Arrow thickness indicates relative likelihood of different transmission routes.

MPX incidence in DRC has increased 20-fold between 1981-1986 and 2006-2007 (38), and countries considered by WHO to be endemic for MPXV have recently expanded to include Nigeria and Cameroon, likely as a result of expanded surveillance (39) and an increase in the susceptible population. Historically, most well-documented cases for which we have phylogenetic information have been infected with Clade 1 MPXV, though there have been increases over time in documentation of infection with Clades 2 and 3 MPXV. Though most outbreaks have involved case counts in the single digits, several recent outbreaks are thought to have been sustained by repeated spillover events (27, 33, 40) and nosocomial transmission (27, 31, 41) rather than human-to-human transmission in the general population (**Figure 3**).

Historically, primary cases resulting from spillover have disproportionately been young children, especially boys (42, 43). This is likely the result of an inverse association observed between age and the likelihood of catching or eating rodents (44). Furthermore, regular smallpox vaccination has been suggested to provide cross-protection against MPXV (45) but ended in the 1970s across much of Sub-Saharan Africa, leaving a large fraction of the population unprotected.

There have been instances of MPXV importation to non-endemic countries, with the most notable being a 2003 outbreak amongst prairie dogs and their human owners in the

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 8 August 2022 doi:10.20944/preprints202208.0128.v1

Midwestern United States (35, 46), as well as several importations resulting from a 2017-18 outbreak in Nigeria (47-50) (**Figure 3**).

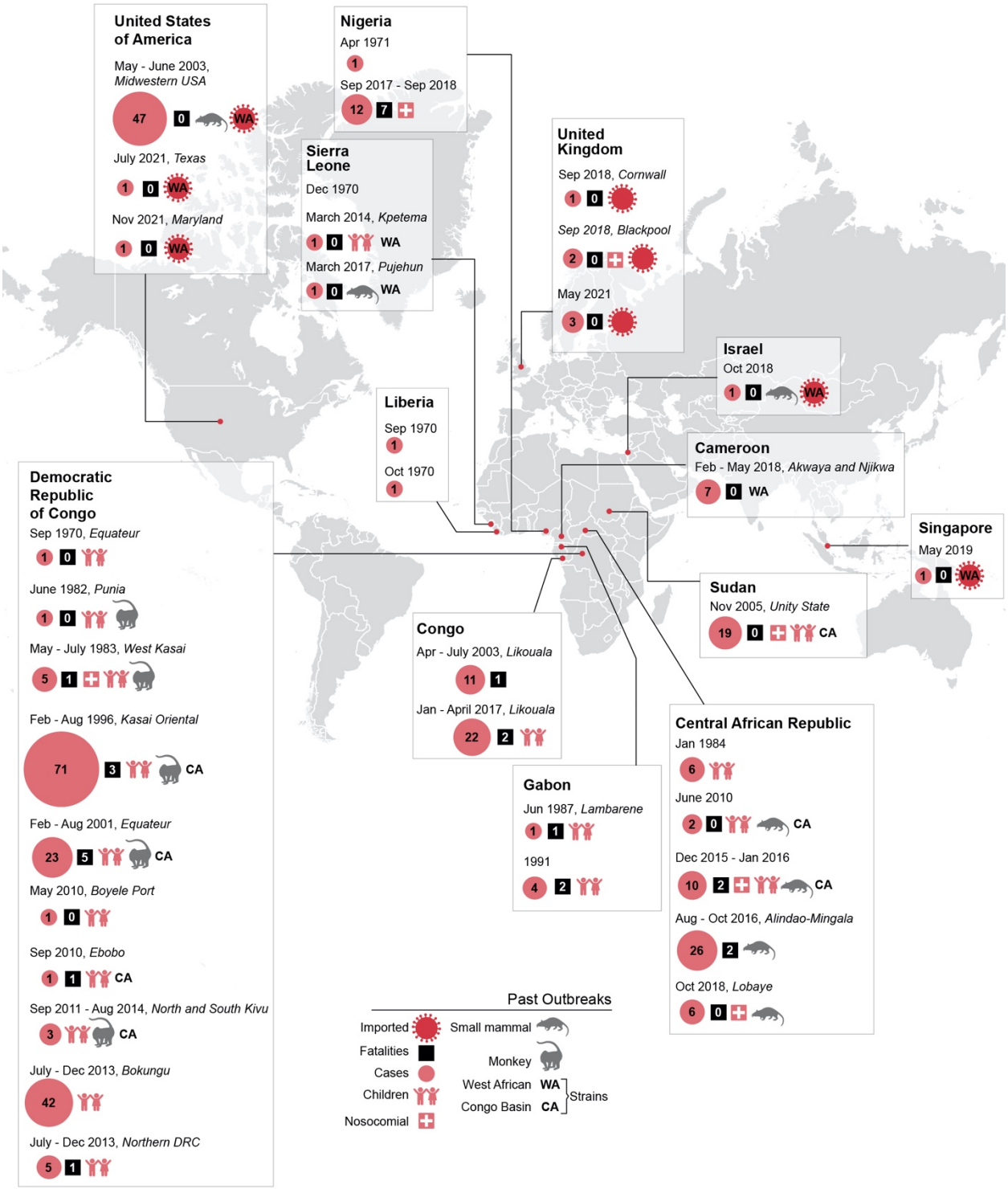

Figure 3. Historical outbreaks of MPX, including imported cases, organized by geographic location. Case numbers, fatalities, MPXV clade, and animal hosts indicated where known. Outbreaks affecting primarily children and/or associated with nosocomial transmission are notated as such.

4. Human-to-Human Transmission

 doi:10.20944/preprints202208.0128.v1

4.1. Epidemiological Dynamics

Estimates of reproduction numbers vary widely for MPXV. An early estimate of 0·815 (45), based on MPX outbreak data in DRC from 1980-1984, suggested that outbreaks are self-limiting in unvaccinated populations. In 2011-2012, the overall prevalence of anti-OPXV antibodies was 51% in Cote d'Ivoire and 60% in DRC, which has likely driven the reproduction number of MPXV below one in these areas (51). Even in individuals not vaccinated against smallpox, seroprevalence of OPXV antibodies was up to 37% in those under age 23 in Ghana, with children from rural forest communities significantly more likely to be seropositive (23), 19% in Cote d'Ivoire, and 26% in DRC (51) in individuals born after 1985.

MPXV remains less transmissible than smallpox, for which convergent reproduction number estimates were around 4-6 (52). The reproduction number for the prodromal period of smallpox was found to be 0·164 for a historical outbreak in Nigeria (53), corroborating the observation that smallpox patients were not particularly infectious before the onset of rash. MPXV has been thought to behave similarly.

Transmission heterogeneity has been documented for MPXV. It has been estimated that the top quintile of infectious patients, determined by transmission data from DRC in 1980-1984, ultimately generate over 60% of subsequent cases (54) while the majority of primary cases fail to infect even one other person (10): 67% of outbreaks in DRC involved only one case (45). However, historical data will likely not accurately represent current trends. Despite the relative infrequency of transmission, there have been instances of superspreading events. In one outbreak, the likely index patient spread MPXV to eight family members (55) while in another instance in DRC, two children infected a total of eight people, none of whom transmitted MPXV onwards (41). Historically, unrecognized or misdiagnosed illness has been the most important determinant of superspreading events (54).

4.2. Routes

In humans, MPXV shedding has been documented in urine, skin lesions (48), nasopharyngeal swabs, seminal fluid (56), and blood (57). Smallpox relied primarily on respiratory droplet transmission (58), with direct contact and fomite transmission playing less dominant roles (59). For MXPV, it is thought that transmission via respiratory droplets, contact with bodily fluids or lesions, and contact with fomites are all possible (21) (**Figure 2A**). Activities that specifically introduce MPXV to the oral mucosa (e.g., eating out of the same dish) are significantly associated with transmission, as opposed to events involving skin-to-skin contact (e.g., helping with bathing) (43). Potential for vertical transmission may exist (60).

Given observed airborne transmission of MPXV between animals, the detection of MPXV in upper respiratory samples (57), and the potential for airborne transmission of smallpox (61, 62), airborne human-to-human transmission of MPXV may be possible. However, epidemiological observations do not support airborne transmission as the dominant route of transmission.

 doi:10.20944/preprints202208.0128.v1

4.3. Determinants of Efficiency

Clade 1 MPXV has been thought to transmit less efficiently than Clades 2 and 3 MPXV based on humans and animal models (63). Existing rodent and NHP models demonstrate that increased inoculation dose led to increased transmission, and more direct inoculation routes led to increased disease severity and transmissibility of MPXV (64, 65). In humans, complex exposures to MPXV-infected prairie dogs, defined as an invasive exposure (e.g., bite or scratch) combined with a non-invasive exposure, led to a compressed disease progression while non-invasive exposures only were associated with typical presentations of MPX (66). These differences in disease progression and potential for onwards transmission likely influence epidemiological metrics such as generation time and reproduction number.

The proportion of those infected with MPXV that experience atypical or subclinical infection remains unclear, and the implications for transmission of non-classically presenting infection are not understood. There has been infrequent or no documentation of infection of contacts of smallpox patients during the prodrome (67), or in the absence of rash (68), respectively. Though epidemiological observations (69) support the idea that MPXV shedding peaks with the onset of the rash, the potential for transmission during the prodromal phase remains (69), with documented transmission to contacts of some patients in the pre-rash period (70).

Atypical MPX presentations resulting from non-traditional exposure routes may also make diagnosis difficult and increase the time from symptom onset (i.e., the putative start of infectiousness) to diagnosis. Even in cases with minimal documentation of unorthodox transmission routes, up to 13% of MPX cases might present atypically (8). Based on historical experiences with delayed diagnosis of smallpox and the resultant increase in transmission risk (54), MPXV transmitted via unusual routes, and thus presenting atypically, may prove more difficult to diagnose, resulting in larger outbreaks.

4.4. Risk Factors

Though specific risk factors vary between outbreaks, the importance of understanding the nuances of specific populations in predicting and anticipating outbreak dynamics cannot be overstated. Historically, MPX cases resulting from human-to-human transmission were more likely to be female, unvaccinated against smallpox, and living in the same residence and/or providing nursing care to a primary case (42). Importantly, these data are based on Clade 1 MPX cases in DRC and may not reflect other endemic areas; documentation from outbreaks across endemic countries indicates that children bear much of the burden of MPX disease (**Figure 3**). In a recent outbreak of Clade 3 MPX in Nigeria, 21–40-year-olds were primarily affected (21), though the index patient was an 11-year-old boy (48, 71). These risk factors indicate the role of behavioral and cultural determinants in facilitating human-to-human transmission of MPXV.

Nosocomial MPXV transmission, both to patients and healthcare workers, remains a serious concern in outbreaks in both endemic and non-endemic regions. Smallpox was associated with nosocomial outbreaks (72), with the highest transmission rates occurring within hospitals (73). Likewise, hospital-associated outbreaks of MPX are especially severe

 doi:10.20944/preprints202208.0128.v1

and long-lasting. This is likely due to a combination of factors, including infections in vulnerable populations, hospital hygiene practice, and the use of aerosol-generating procedures (74). Six generations of MPXV transmission were documented in a hospital in Impfondo, Republic of Congo, indicating MPXV's potential for spread if not quickly addressed in healthcare settings (75). In one incident in the United Kingdom, a healthcare worker who had handled the bedding and clothing of an MPX patient was infected with MPXV (70). Precautions such as the use of appropriate personal protective equipment (PPE), proper waste management practices, and patient isolation should be implemented to minimize hospital transmission of MPXV.

4.5. Countermeasures

There are two U.S. FDA-licensed vaccines against smallpox and monkeypox, ACAM2000 and JYNNEOS (76). It has been posited that the cessation of regular smallpox vaccinations after its eradication has been a contributing factor to rising MPX cases (38). Importantly, ACAM2000 incorporates replication competent live *vaccinia* virus; because of this, ACAM2000 is contraindicated for people living with HIV, regardless of immune status (77), whereas the JYNNEOS vaccine is a replication-deficient *vaccinia* virus vaccine. Replication-competent vaccines could cause clinical infection in humans as well as produce infectious virus that could be transmitted onwards, whereas replication-deficient vaccines do not produce infectious virus in humans, and therefore pose a substantially lower risk of adverse events compared with replication-competent vaccines (78).

Populations at high risk for MPXV infection are often vaccinated prior to exposure – this has historically included lab workers and clinicians. Unfortunately, routine vaccination is not currently available in endemic countries. Post-exposure vaccination can reduce the risk of infection when given within four days of exposure and can reduce the severity of symptoms when given between four and 14 days after exposure (77). However, the time between onset of fever and onset of rash has been shown to be longer, and disease can present as mild or asymptomatic, in vaccinated individuals, potentially altering transmission dynamics (79). The extent of protection against MPXV breakthrough offered by these vaccines remains unclear.

There is currently no specific treatment approved for MPXV infection, though there are several antivirals developed to treat smallpox that are being tested, including tecovirimat, brincidofovir, and cidofovir. In a retrospective study of MPX cases in the United Kingdom from 2018 to 2021, one of seven patients was treated with tecovirimat and experienced a shorter duration of viral shedding (57), indicating that antivirals may help reduce the risk of MPXV transmission.

5. Current Outbreak

5.1. Epidemiology

The 2022 outbreak was first reported in the UK in May, and new cases were rapidly reported in other European countries. Though Europe remains the epicenter of the outbreak, cases have since been detected in the Americas, Oceania, and Asia (6, 80) (**Figure 1A**).

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 8 August 2022 doi:10.20944/preprints202208.0128.v1

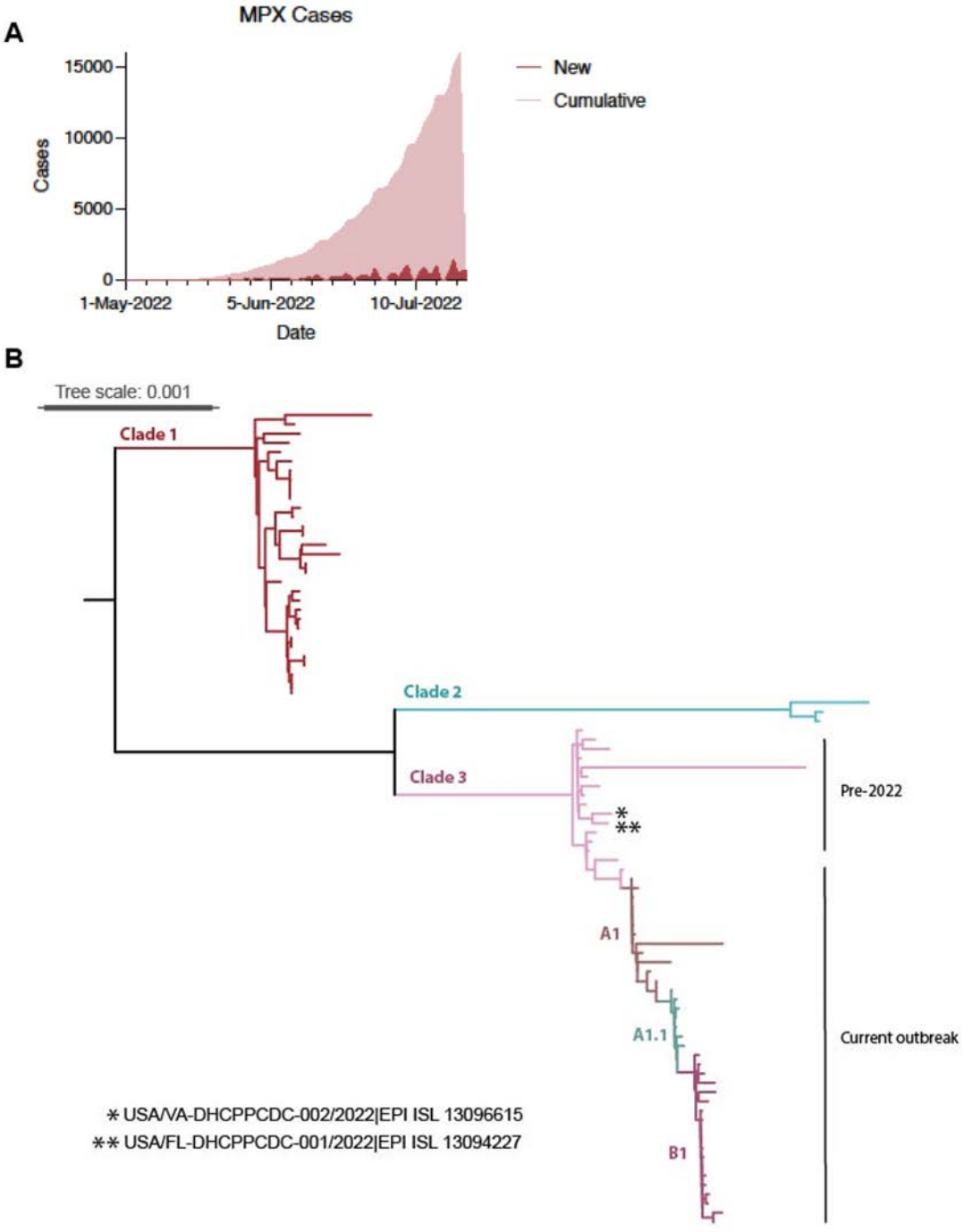

Figure 4. Epidemiology and phylogeny of the current outbreak. **(a)** Epidemic curve of daily new cases and cumulative total cases in non-endemic countries from May 1, 2022 to July 29, 2022. Data was retrieved from Global.health (https://github.com/globaldothealth/monkeypox). **(b)** Phylogenetic trees showing sequences from the current outbreak alongside historical outbreaks. Full length genomes of all variants were obtained from GISAID database (https://www.gisaid.org/) and GenBank (https://www.ncbi.nlm.nih.gov/genbank/) and alignments were made with Muscle (97). Substitution models was determined using ModelGenerator (98) and Maximum likelihood phylogenetic tree was constructed using IG-TREE2 (99) with substitution model F81+F+I. Approximate likelihood-ratio test (aLRT) was used to test branch supports (1000 replicates) and the tree was visualized in Itol (100), and midpoint rooted for purposes of clarity. Only bootstrap values greater than 70% are shown. Bars indicate nucleotide substitutions per site. Clade and lineage are designated according to the nomenclature proposed by Happi et al. (7).

 doi:10.20944/preprints202208.0128.v1

The current outbreak has unfolded atypically in several capacities. CFRs have been low, continuous human-to-human transmission has been observed, and the outbreak remains in the exponential growth phase (**Figure 4A**). An estimate of the reproduction number based on all cases in this outbreak through July 22, 2022 was 1.29, indicating the potential for MPXV's continued spread (81). In contrast to historical importations of MPXV, the first detected cases in this outbreak have not been linked to endemic areas as of July, 2022 (6). Finally, sequencing data indicate that this outbreak is caused by Clade 3 MPXV and is subject to continuous microevolution (**Figure 4B**)(82)

Over 70% of documented cases are in their 20s and 30s (83) and primarily identify as men who have sex with men (MSM). Given the observed patterns of MPXV's spread through sexual networks, and documented instances of *vaccinia* virus transmission via sexual contact (84), it appears likely that sexual interactions at least partially contribute to the continued spread of MPXV in the current outbreak. MPXV DNA was found in seminal fluid at similar levels as shedding from nasopharyngeal swabs in some patients (56), though the pattern of symptoms, especially lesion locations, indicates that sexual contact is the most likely route of transmission (**Figure 2B**). In some cases, MPXV DNA has persisted in inguinoscrotal lesions long after its clearance in other bodily fluids (57).

High-risk sexual behaviors, including unprotected sex and having sex with multiple anonymous or random sexual partners, are a risk factor in the current outbreak. In the early phase of this outbreak, men in whom MPX has been diagnosed had higher rates of HIV infection than the general MSM population, with 14/27 confirmed cases in Portugal from April 29-May 23 being HIV positive (85) and an overall HIV positivity rate of 54·29% in a meta-analysis of 35 cases across five countries (83), signaling sexually promiscuous behavior in these patients. The dense sexual networks and high HIV prevalence rates of this MSM population are likely conducive to the continued spread of MPXV absent stronger public health measures.

Models predicting the course of the current outbreak are inconclusive. One model, assuming transmission within sexual networks and thus based on sexual partnership data in the United Kingdom, predicted a high likelihood of a major (>10,000 total cases) outbreak among the MSM population but low probability of sustained transmission in the non-MSM community in the absence of public health control measures (86). However, an SEIR (susceptible-exposed-infectious-recovered) model using characteristics of a typical high-income European country, but not assuming sexual transmission, found that this outbreak should eventually subside even in the absence of intervention. When accounting for public health measures, the same model found substantial reductions in outbreak size and duration (87). Though the course of this outbreak remains uncertain, the latter model, which does not heavily weigh the potential for sexual transmission in sustaining this outbreak, likely underestimates its expected size and duration. This discrepancy underscores the inability of mathematical models to adequately predict the progression of an outbreak in the early phase when real-life data on transmission routes, prevalence and at-risk populations is missing.

 doi:10.20944/preprints202208.0128.v1

5.2. Atypical Presentation

As stated, misdiagnosis and underdiagnosis of MPX can lead to larger and longer outbreaks. In the current outbreak, there have been multiple reports of the initial misdiagnosis of patients who were later confirmed to have MPX (88, 89) due to atypical clinical manifestation that does not resemble MPX observed in African outbreaks. There have been reports of patients presenting with no rash (90) and no prodrome (88). In cases described in the United Kingdom, 20% of patients with a rash had no prodrome before rash onset, and only 11% of patients even presented with rash (90), the characteristic diagnostic marker for MPX. Estimates of the mean incubation period in the current outbreak have been on the short end of the 7-14 day incubation period range: 7·6 days based on patient data from the United States and the Netherlands (91), and 8·5 days based on cases in the Netherlands only (92).

Frequently in this outbreak, patients presenting atypically with genital or perianal ulcers have been initially misdiagnosed with common sexually transmitted infections (STIs) and sent home with antibiotics (56, 88). In the United States, the average time to diagnosis with an OPXV in the first 17 identified cases of this outbreak was 11 days after rash onset, with one patient seeking medical care four times over an eight-day period and another being diagnosed a full three weeks after appearance of the rash (89). Given the frequency of incorrect initial diagnoses, it is likely that the outbreak both is larger than we currently believe and will continue to increase based on historical patterns of MPXV and smallpox outbreaks. Furthermore, the observed trend of MPX patients making repeated visits to healthcare facilities while actively contagious and undiagnosed increases the risk of healthcare-associated outbreaks.

Several factors likely contribute to the observed increase in atypically presenting MPX cases. Given that transmission routes might affect disease presentation, it is possible that this previously unrecognized mode of transmission results in different clinical disease manifestations than those previously observed. The high rates of HIV coinfection may also contribute: one study found that HIV-positive MPX patients during the 2017-18 outbreak in Nigeria had higher rates of genital ulcers and higher likelihood of presenting with genital rash as the first symptom than did HIV-negative patients (93).

The less severe clinical disease caused by Clades 2 and 3 MPXV may result in some of the less typically presenting cases observed in this outbreak – it is also possible that patients are less likely to seek medical care if they feel well. This is similar to patterns noted in smallpox outbreaks: paradoxically, though *Variola minor* may be less inherently infectious than *Variola major*, *Variola minor* is actually associated with larger, longer, and less rapidly recognized outbreaks (67), likely as a result of its milder presentation leading to increased time to diagnosis and isolation of cases. Likewise, infections with Clade 3 MPXV in this outbreak have had long intervals from symptom onset to diagnosis, leading to increased transmission.

Especially in the early stages of this outbreak, negative stigma associated with sexually promiscuous MSM communities or inexperience with MPX may have made providers more likely to immediately diagnose patients with routine STIs, prescribe

 doi:10.20944/preprints202208.0128.v1

antibiotics, and send them home rather than thoroughly considering the full range of potential differential diagnoses.

6. Conclusions

The burden of MPX has historically fallen primarily on a small number of Sub-Saharan African countries whereas the current outbreak has spread outside traditionally endemic areas and is disproportionately affecting MSM. We have a tenuous idea based on epidemiological observations, but a better understanding of fundamental questions in transmission will help determine evidence-based solutions to mitigate MPXV's spread in both endemic and non-endemic areas. In both endemic and non-endemic areas, more in-depth surveillance and diagnostic methods will provide a richer understanding of the full extent of MPX cases, many of which are likely being overlooked.

In general, high background levels of OPXV antibodies in MPXV endemic areas suggest that many MPX cases go unrecognized. In Africa, MPX is a reportable disease through the Integrated Disease Surveillance and Response System (94), but reporting is likely uneven in the absence of readily available diagnostics. Likewise, the inability to pinpoint the source of the current outbreak or link cases to an endemic area indicates a similar pattern of undetected spread for a substantial period of time. Clearly, further efforts are needed to address the public health burden of MPXV. Differing strategies will need to be employed in endemic and non-endemic areas.

Active and syndromic surveillance methods would provide insight into fluctuations in epidemiological trends, especially in instances where confirmatory diagnostic methods are challenging. Regardless, it is recommended that the development of better diagnostics be prioritized, both point-of-care diagnostics that can be done outside of a healthcare facility as well as diagnostic approaches in healthcare settings, to reduce misdiagnosis. In particular, the success of rapid antigen tests seen during the SARS-CoV-2 pandemic provides a framework for scaling up the development and distribution of point of care diagnostics.

Given that children bear the burden of MPX cases in endemic areas, educating healthcare providers on the features that distinguish MPX from chickenpox will also help facilitate timely and accurate diagnoses, allowing for faster isolation and behavior change. Targeted vaccination of populations at risk for spillover events (e.g., children in forested areas) or healthcare workers may be crucial to stemming outbreaks. Educating people on how to prevent spillover and protect children will be key to reducing both the incidence and size of MPX outbreaks, as well as other zoonoses. Taking into consideration the current spread of MPXV in non-endemic countries and the social stigma and marginalization associated with being a member of the LGBTQ+ community in endemic regions, it seems plausible that similar spread in at-risk adult populations may occur undetected in these areas. Thus, safe access to inclusive healthcare could be crucial to address this gap.

We still lack clear information on specific routes of animal-to-human transmission, as well as the range of potential reservoir hosts. The potential for a peridomestic cycle of MPXV, and the implications of such a cycle, are also unknown. Furthermore, factors

 doi:10.20944/preprints202208.0128.v1

facilitating transmission from a primary case to the rest of the family are unclear. Finally, most historical research on MPXV has focused predominantly on data from Clade 1 MPXV in DRC; the behavior of Clades 2 and 3 MPXV is less well understood. Further research on all these topics will allow for more targeted education and prevention efforts that allow at-risk communities to take specific action to lower the risk of spillover and ongoing transmission.

In the current outbreak, which as of now is primarily affecting sexually promiscuous MSM populations and may not be sustained in the general population, targeted approaches will be helpful. Vaccination of at-risk populations, including sex workers or those on PrEP, as a proxy for sexual promiscuity, might be crucial to preventing the further spread of this outbreak. Discussions about risky sexual behaviors and how to reduce risk could be helpful, especially in collaboration with community leaders. Given that many cases in this outbreak present atypically, expanding the case definition for MPX and educating healthcare providers on the broad range of clinical presentations of MPX, as well as features that distinguish MPX from common STIs, will be crucial. Active surveillance methods will also capture a larger proportion of those with MPX, helping provide a fuller understanding of the extent of this outbreak.

It remains unclear what proportion of cases in this outbreak present atypically and to what extent asymptomatic or atypical cases contribute to transmission. Furthermore, it is unknown whether transmission in sexual networks is the result of contact with lesions during sex or whether it is a result of true sexual fluid (i.e., seminal) transmission. Though MPXV is clearly spreading efficiently through networks of MSM, the transmission efficiency in heterosexual relationships or between women who have sex with women continues to be unclear. In addition, with the rapid increase in cases, the likelihood of transmission beyond networks of MSM increases dramatically. The observed microevolution of MPXV during the current outbreak is suggestive of long unrecognized circulation of MPXV in the human population. In addition, the adaptation of MPXV to humans will likely result in more efficient replication and human-to-human transmission (82).

Addressing these questions will allow for more targeted public health interventions as well as a better understanding of whether this outbreak might be propagated in the general population. It is clear from the body of HIV/AIDS research that increased stigma towards those living with HIV is significantly associated with lower levels of medication adherence and usage of health services (95). Working in conjunction with the media to send a message that though MSM have thus far been especially affected in the current outbreak, MPX is not a disease of MSM and being an MSM is not in itself a risk factor will be vital to reducing stigma. However, targeted interventions will be complicated in parts of the world where same-sex relationships are illegal (96). At the same time, however, it is clear that targeted interventions stand to be the most beneficial. Working with established leaders in MSM communities and at-risk communities in endemic countries to establish mutually trusting relationships, with the goal of developing feasible and

 doi:10.20944/preprints202208.0128.v1

sensitive interventions, is key to addressing both the current outbreak of MPX and future MPX cases in endemic areas.

7. Search Strategy and Selection Criteria

We reviewed PubMed and Google Scholar using search terms that included "monkeypox", "monkeypox transmission", "smallpox", and "smallpox transmission" (up to July 22, 2022). PubMed notifications for the search term "monkeypox" were established to capture relevant literature related to the current outbreak. References of potential interest in articles were also included regardless of whether they were captured with the PubMed and Google Scholar search terms. Titles and abstracts of articles were first reviewed to determine whether a) the study was about monkeypox or smallpox and b) it addressed the current or a historical outbreak, transmission between animals, transmission between humans, spillover events, or epidemiological data. This process yielded the 86 journal articles included here; other references were included based on relevance to the current outbreak. Studies were categorized by topic, with three categories: smallpox, monkeypox, and specifically the current monkeypox outbreak. We then synthesized important topics in monkeypox transmission based on the full text of these studies.

Author Contributions: Writing – original draft preparation, JCR; writing – review and editing, JCR, VJM, and JRP.

Funding: This work was supported by the Intramural Research Program of the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH).

Acknowledgments: We would like to thank Ryan Kissinger (Visual and Medical Arts, RML) for his rapid, professional, and artistic figures he designed for us, which highlight the main concepts presented in this review, and Rose Perry-Gottschalk for her assistance. We would also like to thank Kwe Claude Yinda for his expertise on viral meta-genomics and generation of the phylogenetic tree, and Neeltje van Doremalen for her insightful feedback and editorial suggestions on the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Adalja A IT. A Novel International Monkeypox Outbreak. Annals of Internal Medicine. 2022.
2. CDC. 2022 Monkeypox and Orthopoxvirus Outbreak Global Map. Centers for Disease Control and Prevention2022.
3. Essbauer S PM, Meyer H. Zoonotic poxviruses. Veterinary Microbiology. 2010:229-36.
4. Brown K LP. Human Monkeypox: Current State of Knowledge and Implications for the Future. Tropical Medicine and Infectious Disease. 2016.
5. Bunge E HB, Chen L, Lienert F, Weidenthaler H, Baer L, Steffen R. The changing epidemiology of human monkeypox – A potential threat? A systematic review. PLoS Neglected Tropical Diseases. 2022.
6. WHO. Multi-country monkeypox outbreak in non-endemic countries. World Health Organization2022.
7. Christian Happi IA, Placide Mbala, Richard Njouom, Emmanuel Nakoune, Anise Happi, Nnaemeka Ndodo, Oyeronke Ayansola, Gerald Mboowa, Trevor Bedford, Richard A. Neher, Cornelius Roemer, Emma Hodcroft, Houriiyah Tegally, Áine O'Toole, Andrew Rambaut, Oliver Pybus, Moritz U.G. Kraemer, Eduan Wilkinson, Joana Isidro, Vítor Borges, Miguel Pinto, João Paulo Gomes, Cheryl Baxter, Richard Lessells, Ahmed E. Ogwell, Yenew Kebede, Sofonias K. Tessema, Tulio de Oliveira. Urgent need for a non-discriminatory and non-stigmatizing nomenclature for monkeypox virus virological.org: virological.org; 2022 [Available from: https://virological.org/t/urgent-need-for-a-non-discriminatory-and-non-stigmatizing-nomenclature-for-monkeypox-virus/853/1.

 doi:10.20944/preprints202208.0128.v1

8. Breman J RK, Steniowski M, Zanotta E, Gromyko A, Arita I. Human monkeypox, 1970-79. Bulletin of the World Health Organization. 1980:165-82.

9. Likos AM, Sammons SA, Olson VA, Frace AM, Li Y, Olsen-Rasmussen M, et al. A tale of two clades: monkeypox viruses. J Gen Virol. 2005;86(Pt 10):2661-72.

10. Jezek Z MS, Mutumbo M, Nakano J, Paluku K, Szczeniowski M. Human monkeypox: a study of 2,510 contacts of 214 patients. Journal of Infectious Disease. 1986:551-5.

11. Hammarlund E LM, Carter S, Amanna I, Hansen S, Strelow L, Wong S, Yoshihara P, Hanifin J, Slifka M. Multiple diagnostic techniques identify previously vaccinated individuals with protective immunity against monkeypox. Nature Medicine. 2005:1005-11.

12. Doshi R GS, Doty J, Babeaux A, Matheny A, Burgado J, Townsend M, Morgan C, Satheshkumar S, Ndakala N, Kanjingankolo T, Kitembo L, Malekani J, Kalemba L, Pukuta E, N'kaya T, Kangoula F, Moses C, McCollum A, Reynolds M, Mombouli J, et al. Epidemiology and Ecologic Investigations of Monkeypox, Likouala Department, Republic of the Congo, 2017. Emerging Infectious Diseases. 2019.

13. Doty J MJ, Kalemba L, Stanley W, Monroe B, Nakazawa Y, Mauldin M, Bakambana T, Liyandja T, Braden Z, Wallace R, Malekani D, McCollum A, Gallardo-Romero N, Kondas A, Peterson A, Osorio J, Rocke T, Karem K, Emerson G, Carroll D. Assessing Monkeypox Virus Prevalence in Small Mammals at the Human-Animal Interface in the Democratic Republic of the Congo. Viruses. 2017.

14. Falendysz E LJ, Doty J, Nakazawa Y, Crill C, Lorenzsonn F, Kalemba L, Ronderos M, Mejia A, Malekani J, Karem K, Carroll D, Osorio J, Rocke T. Characterization of Monkeypox virus infection in African rope squirrels (Funisciurus sp.). PLoS Neglected Tropical Diseases. 2017.

15. Falendysz E LJ, Lorenzsonn F, Salzer J, Hutson C, Doty J, Gallardo-Romero N, Carroll D, Osorio J, Rocke T. Further Assessment of Monkeypox Virus Infection in Gambian Pouched Rats (Cricetomys gambianus) Using In Vivo Bioluminescent Imaging. PLoS Neglected Tropical Diseases. 2015.

16. Guarner J JB, Paddock C, Shieh W, Goldsmith C, Reynolds M, Damon I, Regnery R, Zaki S. Monkeypox Transmission and Pathogenesis in Prairie Dogs. Emerging Infectious Diseases. 2004.

17. Hutin Y WR, Malfait P, Pebody R, Loparev V, Ropp S, Rodriguez M, Knight J, Tshioko F, Khan A, Szczeniowski M, Esposito J. Outbreak of Human Monkeypox, Democratic Republic of Congo, 1996-1997. Emerging Infectious Diseases. 2001.

18. Radonic A MS, Dabrowski P, Couacy-Hymann E, Schuenadel L, Kurth A, Matz-Rensing K, Boesch C, Leendertz F, Nitsch A. Fatal Monkeypox in Wild-Living Sooty Mangabey, Cote d'Ivoire, 2012. Emerging Infectious Diseases. 2014.

19. Khodakevich L JZ, Kinzanzka K. Isolation of monkeypox virus from wild squirrel infected in nature. The Lancet. 1986.

20. Patrono L PK, Samuni L, Ulrich M, Rothemeier C, Sachse A, Muschter S, Nitsche A, Couacy-Hymann E, Boesch C, Wittig R, Calvignac-Spencer S, Leendertz F. Monkeypox virus emergence in wild chimpanzees reveals distinct clinical outcomes and viral diversity. Nature Microbiology. 2020:955-65.

21. Alakunle E MU, Nchinda G, Okeke M. Monkeypox Virus in Nigeria: Infection Biology, Epidemiology, and Evolution. Viruses. 2020.

22. Salzer J CD, Rwego I, Li Y, Falendysz E, Shisler J, Karem K, Damon I, Gillespie T. Serologic evidence for circulating orthopoxviruses in peridomestic rodents from rural Uganda. Journal of Wildlife Diseases. 2013:125-31.

23. Reynolds M CD, Olson V, Hughes C, Galley J, Likos A, Montgomery J, Suu-Ire R, Kwasi M, Root J, Braden Z, Abel J, Clemmons C, Regnery R, Karem K, Damon I. A Silent Enzootic of an Orthopoxvirus in Ghana, West Africa: Evidence for Multi-Species Involvement in the Absence of Widespread Human Disease. The American Journal of Tropical Medicine and Hygiene. 2010:746-54.

 doi:10.20944/preprints202208.0128.v1

24. Fuller T TH, Mulembakani P, Johnston S, Lloyd-Smith J, Kisalu N, Lutete T, Blumberg S, Fair J, Wolfe N, Shongo R, Formenty P, Meyer H, Wright L, Muyembe J, Buermann W, Saatchi S, Okitolonda E, Hensley L, Smith T, Rimoin A. Using Remote Sensing to Map the Risk of Human Monkeypox Virus in the Congo Basin. EcoHealth. 2010:14-25.

25. Thomassen H FT, Asefi-Najafabady S, Shiplacoff J, Mulembakani P, Blumberg S, Johnston S, Kisalu N, Kinkela T, Fair J, Wolfe N, Shongo R, LeBreton M, Rimoin A. Pathogen-Host Associations and Predicted Range Shifts of Human Monkeypox in Response to Climate Change in Central Africa. PLoS ONE. 2013.

26. Reynolds M DJ, McCollum A, Olson V, Nakazawa Y. Monkeypox re-emergence in Africa: a call to expand the concept and practice of One Health. Expert Review of Anti-Infective Therapy. 2019:129-39.

27. Yinka-Ogunleye A AO, Dalhat M, Ongoina D, et al. Outbreak of human monkeypox in Nigeria in 2017-18: a clinical and epidemiological report. The Lancet Infectious Diseases. 2019:872-9.

28. Jezek Z, Nakano JH, Arita I, Mutombo M, Szczeniowski M, Dunn C. Serological survey for human monkeypox infections in a selected population in Zaire. J Trop Med Hyg. 1987;90(1):31-8.

29. Erez N AH, Milrot E, Schwartz Y, Wiener-Nell Y, Paran N, Politi B, Tamir H, Israely T, Weiss S, Beth-Din A, Shifman O, Israeli O, Yitzhaki S, Shapira S, Melamed S, Schwartz E. Diagnosis of Imported Monkeypox, Israel, 2018. Emerging Infectious Diseases. 2019.

30. Berthet N NE, Whist E, Selekon B, Pharm A, Manugerra J, Gessain A, Kazanji M. Maculopapular lesions in the Central African Republic. The Lancet. 2011:1354.

31. Besombes C GE, Konamna X, Selekon B, Gessain A, Berthet N, Manuguerra J, Fontanet A, Nakoune E. Intrafamily Transmission of Monkeypox Virus, Central African Republic, 2018. Emerging Infectious Diseases. 2019.

32. Khodakevich L JZ, Messinger D. Monkeypox viurs: ecology and public health significance. Bulletin of the World Health Organization. 1988:747-52.

33. McCollum A NY, Ndongala G, Pukuta E, et al. Human Monkeypox in the Kivus, a Conflict Region of the Democratic Republic of the Congo. The American Journal of Tropical Medicine and Hygiene. 2015:718-21.

34. Meyer H PM, Stemmler M, Emmerich P, Schmitz H, Varaine F, Shungu R, Tshioko F, Formenty P. Outbreaks of Disease Suspected of Being Due to Human Monkeypox Virus Infection in the Democratic Republic of Congo in 2001. Journal of Clinical Microbiology. 2002.

35. Reed K MJ, Graham M, Regnery R, Sotir M, Wegner M, Kazmierczak J, Stratman E, Li Y, Fairley J, Swain G, Olson V, Sargent E, Kehl S, Frace M, Kline R, Foldy S, Davis J, Damon I. The detection of monkeypox in humans in the Western Hemisphere. New England Journal of Medicine. 2004:342-50.

36. Nalca A LV, Garza N, Zumbrun E, Frick O, Chapman J, Hartings J. Experimental Infection of Cynomolgus Macaques (Macaca fascicularis) with Aerosolized Monkeypox Virus. PLoS ONE. 2010.

37. Heberling R KS. Induction, Course, and Transmissibilty of Monkeypox in the Baboon (Papio cynocephalus). The Journal of Infectious Diseases. 1971:33-8.

38. Rimoin A MP, Johnston S, Muyembe J. Major increase in human monkeypox incidence 30 years after smallpox vaccination campaigns cease in the Democratic Republic of Congo. PNAS. 2010:16262-7.

39. Beer E RB. A systematic review of the epidemiology of human monkeypox outbreaks and implications for outbreak strategy. PLoS Neglected Tropical Diseases. 2019.

40. Sadeuh-Mba SA, Yonga MG, Els M, Batejat C, Eyangoh S, Caro V, et al. Monkeypox virus phylogenetic similarities between a human case detected in Cameroon in 2018 and the 2017-2018 outbreak in Nigeria. Infect Genet Evol. 2019;69:8-11.

41. Nakoune E LE, Ndjapou S, Janssens C, Zuniga I, Van Herp M, Fongbia J, et al. A Nosocomial Outbreak of Human Monkeypox in the Central African Republic. Open Forum Infectious Diseases. 2017.

42. Jezek Z GB, Szczeniowski M, Paluku K, Mutombo M. Clinical-epidemiological features of monkeypox patients with an animal or human source of infection. Bulletin of the World Health Organization. 1988:459-64.

 doi:10.20944/preprints202208.0128.v1

43. Nolen L OL, Katomba J, Likofata J, Mukadi D, Monroe B, Doty J, Kalemba L, Malekani J, et al. Introduction of Monkeypox into a Community and Household: Risk Factors and Zoonotic Reservoirs in the Democratic Republic of the Congo. The American Journal of Tropical Medicine and Hygiene. 2015:410-5.

44. Quiner C MC, Monroe B, Nakazawa Y, Doty J, Hughes C, McCollum A, Ibata S, Malekani J, Okitolonda E, Carroll D, Reynolds M. Presumptive risk factors for monkeypox in rural communities in the Democratic Republic of the Congo. PLoS ONE. 2017.

45. Fine P ZJ, B Grab, H Dixon. The Transmission Potential of Monkeypox Virus in Human Populations. International Journal of Epidemiology. 1988:643-50.

46. Kile J FA, Beard B. Transmission of monkeypox among persons exposed to infected prairie dogs in Indiana in 2003. JAMA Pediatrics. 2005:1022-5.

47. Vaughan A AE, Astbury J, Balasegaram S, et al. Two cases of monkeypox imported to the United Kingdom, September 2018. Eurosurveillance. 2018.

48. Hobson G AJ, Adler H, Firth R, Gould S, Houlihan C, Johnson C, Porter D, Rampling T, Ratcliffe L, Russell K, Shankar A, Wingfield T. Family cluster of three cases of monkeypox imported from Nigeria to the United Kingdom, May 2021. Eurosurveillance. 2021.

49. Yong S NO, Ho Z, Mak T, Marimuthu K, Vasoo S, Yeo T, Ng Y, Cui L, Ferdous Z, et al. Imported Monkeypox, Singapore. Emerging Infectious Diseases. 2020:1826-30.

50. Health MDo. Travel-Associated Monkeypox virus infection confirmed in Maryland resident. Baltimore: Maryland Department of Health Newsroom; 2021.

51. Leendertz S SD, Theophil D, Anoh E, Mossoun A, Schubert G, Wiersma L, Akoua-Koffi C, Couacy-Hymann E, Muyembe-Tamfum J, Karhemere S, Pauly M, Schrick L, Leendertz F, Nitsche A. A Cross-Sectional Serosurvey of Anti-Orthopoxvirus Antibodies in Central and Western Africa. Viruses. 2017.

52. R Gani SL. Transmission potential of smallpox in contemporary populations. Nature. 2001:748-51.

53. Eichner M DK. Transmission Potential of Smallpox: Estimates Based on Detailed Data from an Outbreak. American Journal of Epidemiology. 2003:110-7.

54. Lloyd-Smith J SS, Kopp P, Getz W. Superspreading and the effect of individual variation on disease emergence. Nature. 2005:355-9.

55. Mwamba P TK, Moudi A, Mukinda V, Mwema G, Messinger D, et al. Human Monkeypox – Kasai Oriental, Zaire, 1996-1997. Morbidity and Mortality Weekly Report; 1997.

56. Antinori A MV, Vita S, Carletti F, Tacconi D, Lapini L, et al. Epidemiological, clinical, and virological characteristics of four cases of monkeypox support transmission through sexual contact, Italy, May 2022. Eurosurveillance. 2022.

57. Adler H GS, Hine P, Snell L, Wong W, Houlihan C, Osborne J, Rampling T, et al. Clinical features and management of human monkeypox: a retrospective observational study in the UK. The Lancet Infectious Diseases. 2022.

58. Breman J HD. Diagnosis and Management of Smallpox. The New England Journal of Medicine. 2002:1300-8.

59. CDC. How does smallpox spread? Centers for Disease Control and Prevention2016.

60. Mbala P HJ, Riu-Rovira T, Ahuka S, Mulembakani P, Rimoin A, Martin J, Muyembe J. Maternal and Fetal Outcomes Among Pregnant Women With Human Monkeypox Infection in the Democratic Republic of Congo. The Journal of Infectious Diseases. 2017:824-8.

61. Millard C. Aerial Convection from Smallpox Hospitals. British Medical Journal. 1944:628-9.

62. Wehrle P PJ, Richter K, Henderson D. An airborne outbreak of smallpox in a German hospital and its significance with respect to other recent outbreaks in Europe. Bulletin of the World Health Organization. 1970:669-79.

63. Hutson C CD, Gallardo-Romero N, Weiss S, Clemmons C, Hughes C, Salzer J, Olson V, Abel J, Karem K, Damon I. Monkeypox Disease Transmission in an Experimental Setting: Prairie Dog Animal Model. PLoS ONE. 2011.

 doi:10.20944/preprints202208.0128.v1

64. Hutson C CD, Self J, Weiss S, Hughes C, Braden Z, Olson V, Smith S, Karem K, Regnery R, Damon I. Dosage comparison of Congo Basin and West African strains of monkeypox virus using a prairie dog animal model of systemic orthopoxvirus disease. Virology. 2010:72-82.

65. Hutson C G-RN, Carroll D, Clemmons C, Salzer J, Nagy T, Hughes C, Olson V, Karem K, Damon I. Transmissibility of the Monkeypox Virus Clades via Respiratory Transmission: Investigation Using the Prairie Dog-Monkeypox Virus Challenge System. PLoS ONE. 2013.

66. Reynolds M YK, Kuehnert M, Davidson W, Huhn G, Holman R, Damon I. Clinical Manifestations of Human Monkeypox Influenced by Route of Infection. The Journal of Infectious Diseases. 2006:773-80.

67. Mack T. Smallpox in Europe, 1950-1971. The Journal of Infectious Diseases. 1972:161-9.

68. A Downie LSV, G Meiklejohn, N Ratnakannan, A Rao, G Krishnan, C Kempe. Studies on the virus content of mouth washings in the acute phase of smallpox. Bulletin of the World Health Organization. 1961:49-53.

69. L Nolen LO, J Katomba, J Likofata, D Mukadi, B Monroe, J Doty, C Hughes, et al. Extended Human-to-Human Transmission during a Monkeypox Outbreak in the Democratic Republic of the Congo. Emerging Infectious Diseases. 2016.

70. Vaughan A AE, Astbury J, Brooks T, Chand M, Flegg P, Hardman A, et al. Human-to-Human Transmission of Monkeypox Virus, United Kingdom, October 2018. Emerging Infectious Diseases. 2020.

71. Ogoina D IJ, Ogunleye A, Ederiane E, Anebonam U, et al. The 2017 human monkeypox outbreak in Nigeria - report of outbreak experience and response in the Niger Delta University Teaching Hospital, Bayelsa State, Nigeria. PLoS One. 2019.

72. CDC. Smallpox – Stockholm, Sweden, 1963. Morbidity and Mortality Weekly Report; 1963.

73. Kiang K KM. Rates and risks of transmission of smallpox and mechanisms of prevention. Journal of Laboratory and Clinical Medicine. 2003:229-38.

74. Judson S MV. Nosocomial Transmission of Emerging Viruses via Aerosol-Generating Medical Procedures. Viruses. 2019.

75. Learned L RM, Wassa Wassa D, et al. Extended interhuman transmission of monkeypox in a hospital community in the Republic of the Congo, 2003. The American Journal of Tropical Medicine and Hygiene. 2005:428-34.

76. Monkeypox and Smallpox Vaccine Guidance. CDC2022.

77. Considerations for Monkeypox Vaccination. CDC2022.

78. Rao AK, Petersen BW, Whitehill F, Razeq JH, Isaacs SN, Merchlinsky MJ, et al. Use of JYNNEOS (Smallpox and Monkeypox Vaccine, Live, Nonreplicating) for Preexposure Vaccination of Persons at Risk for Occupational Exposure to Orthopoxviruses: Recommendations of the Advisory Committee on Immunization Practices - United States, 2022. MMWR Morb Mortal Wkly Rep. 2022;71(22):734-42.

79. Damon I. Status of human monkeypox: clinical disease, epidemiology, and research. Vaccine. 2011:D54-D9.

80. Epidemiological update: Monkeypox multi-country outbreak. European Centre for Disease Prevention and Control; 2022.

81. Du Z, Shao Z, Bai Y, Wang L, Herrera-Diestra JL, Fox SJ, et al. Reproduction number of monkeypox in the early stage of the 2022 multi-country outbreak. medRxiv. 2022:2022.07.26.22278042.

82. Isidro J BV, Pinto M, Sobral D, Santos J, Nunes A, Mixao V, Ferreira R, Santos D, Duarte S. Phylogenomic characterization and signs of microevolution in the 2022 multi-country outbreak of monkeypox virus. Nature Medicine. 2022.

83. Bragazzi N KJ, Mahroum N, Tsigalou C, Khamisy-Farah R, Converti M, Wu J. Epidemiological trends and clinical features of the ongoing mokeypox epidemic: a preliminary pooled data analysis and literature review. Journal of Medical Virology. 2022.

84. CDC. Secondary and tertiary transmission of vaccinia virus after sexual contact with a smallpox vaccinee – San Diego, California, 2012. San Diego: Morbidity and Mortality Weekly Report; 2013.

85. Duque M RS, Martins J, Casaca P, Leite P, Tavares M, Mansinho K, et al. Ongoing monkeypox virus outbreak, Portugal, 29 April to 23 May 2022. Eurosurveillance. 2022.

86. Endo A MH, Abbott S, Ratnayake R, Pearson C, Edmunds W, Fearon E, Funk S. Heavy-tailed sexual contact networks and the epidemiology of monkeypox outbreak in non-endemic regions, May 2022. 2022.

87. Bisanzio D RR. Projected burden and duration of the 2022 Monkeypox outbreaks in non-endemic countries. The Lancet Microbe. 2022.

88. Heskin J BA, Milne C, Brown N, Walters Y, Scott C, Bracchi M, Moore L, Mughal N, Rampling T, Winston A, Nelson M, Duncan S, Jones R, Price D, Mora-Peris B. Transmission of monkeypox virus through sexual contact – A novel route of infection. Journal of Infection. 2022.

89. Minhaj F OY, Whitehill F, Schultz J, Foote M, Davidson W, Hughes C, et al. Monkeypox Outbreak – Nine States, May 2022. Morbidity and Mortality Weekly Report; 2022.

90. Girometti N BR, Bracchi M, Heskin J, McOwan A, Tittle V, Gedela K, et al. Epidemiological Characteristics and Clinical Features of Confirmed Human Monkeypox Virus Cases in Individuals Attending a Sexual Health Centre in London, United Kingdom. The Lancet. 2022.

91. Charniga K MN, Slayton R, Gosdin L, Minhaj F, Philpott D, Smith D, Gearhart S, et al. Estimating the incubation period of monkeypox virus during the 2022 multi-national outbreak. 2022.

92. Miura F EC, Backer J, Xiridou M, Franz E, Coul E, Brandwagt D, van Cleef B, et al. Estimated incubation period for monkeypox cases confirmed in the Netherlands, May 2022. Eurosurveillance. 2022.

93. Ogoina D IM, James H, Oladokun R, Yinka-Ogunleye A, Wakama P, et al. Clinical Course and Outcome of Human Monkeypox in Nigeria. Clinical Infectious Diseases. 2020:210-4.

94. National Technical Guidelines for Integrated Disease Surveillance and Response. Monrovia; 2021.

95. Rueda S MS, Chen S, Gogolishvili D, Globerman J, Chambers L, Wilson M, Logie C, Shi Q, Morassaei S, Rourke B. Examining the associations between HIV-related stigma and health outcomes in people living with HIV/AIDS: a series of meta-analyses. BMJ Open. 2016.

96. Mendos LR. State-Sponsored Homophobia 2019. International Lesbian, Gay, Bisexual, Trans and Intersex Association; 2019.
1.