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Review Article

The evolving monkeypox outbreak amongst homosexual and bisexual transmission: A systematic review

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Abstract

Monkeypox is a viral zoonotic disease. It has evolved into human-to-human transmission with similar characteristics to smallpox. In contrast with the previous endemic outbreak, this 2022 multinational outbreak found numerous data of different skin lesions, predilections and populations. Furthermore, recent findings regarding monkeypox revealed the possibility of sexual transmission.

As a basis for future monkeypox diagnosis guidelines, providing comprehensive data on the symptoms, predilections, age at presentation, previous history of sexual activities, comorbidities, range of incubation period from the time of sexual activity until the symptoms occurred, as criteria for diagnosis of sexual transmitted disease.

We performed a comprehensive research on the outbreak of monkeypox disease in 2022 regarding the route of transmission from inception up until September 2022.

There were 1310 patients from 10 studies who had monkeypox disease in 2022. Patients were mostly found in European countries, with average aged in their 30s, and were 99.54% male. Vesiculopustular lesions and ulcers with central umbilication that appeared prior to prodromal signs were characteristic. Approximately 90% were transmitted during sexual intercourse and in the homosexual group (MSM/ Men who have sex with men), and 5-10% between bisexuals. Approximately 40.84% cases also had HIV as a comorbid disease and 15.42% had concurrent or history of sexually transmitted infection (STI) including syphilis, gonorrhea, chlamydia, herpes simplex, mixed, and other STIs.

Homosexual and bisexual populations we are the most high risk populations in the 2022 outbreak of monkeypox disease. The epidemiology, clinical manifestation, and type of skin lesion were different from the previous outbreak. The findings in this review may supplement information to further establish clinical guidelines on the new presentation of monkeypox disease. Further large-scale studies are necessary to further describe and verify the data with higher levels of evidence.

Key words
Monkeypox; Homosexuals; MSM; STI; Systematic Review.

Introduction

Monkeypox is an infectious disease caused by the monkeypox virus, which belongs to the Poxviridae family.[1] It is a viral infection characterized by enveloped double-stranded DNA.[1-2] The disease was first reported in 1970 and has been endemic in the Congo Basin and West Africa.[2] In September 2018, the United Kingdom reported its first two cases of monkeypox in individuals who had traveled to endemic countries and contracted the virus through animal-to-human transmission.[2] Since

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May 2022, the monkeypox outbreak has been declared a Public Health Emergency of International Concern by the World Health Organization (WHO). During the period from January 1st, 2022 to June 2022, there were 3413 confirmed cases and one death reported in 50 countries/territories across five WHO Regions.[3] This outbreak has exhibited different characteristics compared to previous monkeypox outbreaks. In August 2022, a case of monkeypox was confirmed in an Indonesian citizen who had traveled to several European countries. The patient displayed genital and anal lesions, although there was no history of sexual contact.[4]

In previous African outbreaks, the virus was transmitted from animals to humans, with various animals identified as carriers.[1,3] In humans, the disease progresses in phases, starting with flu-like symptoms and lymphadenopathy. Cutaneous lesions appear later and go through different stages before resolving within 5 to 21 days.[5]

In the 2022 multinational outbreak, human-to-human transmission, particularly through contact with infected lesions, was the main mode of transmission.[1-2] There were also indications of possible sexual transmission, with a high number of cases reported in MSM and bisexual populations, and lesions predominantly occurring in the genital and perianal areas.[1,6] However, further investigation is needed to draw definitive conclusions about these findings.[7] Some cases in MSM and bisexuals also had comorbidities like HIV and other sexually transmitted diseases.[8,9]

The outbreak in 2022 primarily affected sexually active MSM and bisexual individuals, with symptoms including lymphadenopathy in the inguinal region and skin lesions in various body parts, including the genital and perianal regions.[6-9] These symptoms often appeared within 7 days after intimate contact or sexual activity, which is within the typical incubation period of monkeypox.[9] Given these new findings, a systematic literature review is being conducted to explore sexual transmission, changes in epidemiology, clinical manifestations, and lesion types in MSM and bisexuals with monkeypox. The results of this review may contribute to the development of clinical guidelines for the new presentation of monkeypox disease.

Methods

Search strategy Our search strategy involved conducting a thorough search using relevant keywords to assess the outbreak of monkeypox disease in 2022, specifically focusing on the route of transmission through sexual contact, particularly in bisexual and homosexual cases. We searched electronic databases such as PubMed, Cochrane Central Database, ClinicalTrials.gov, and Mendeley from the inception of these databases until August 2022. The search terms included "Monkeypox" or "Mpxv" or "Pox Virus" and "Homosexual" and "Bisexual" and "MSM" and "2022," along with their synonyms.

The retrieved records were then evaluated systematically based on predetermined inclusion and exclusion criteria. Three authors (MT, RA, and LA) independently conducted the initial search by scanning all abstracts to identify relevant studies. In case of discrepancies, the final judgment and eligibility assessment from full-text articles were made by the other two authors (HN and DP), following a similar process to resolve potential disagreements. The systematic reviews flowchart of the literature search strategy is presented in **Figure 1**, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

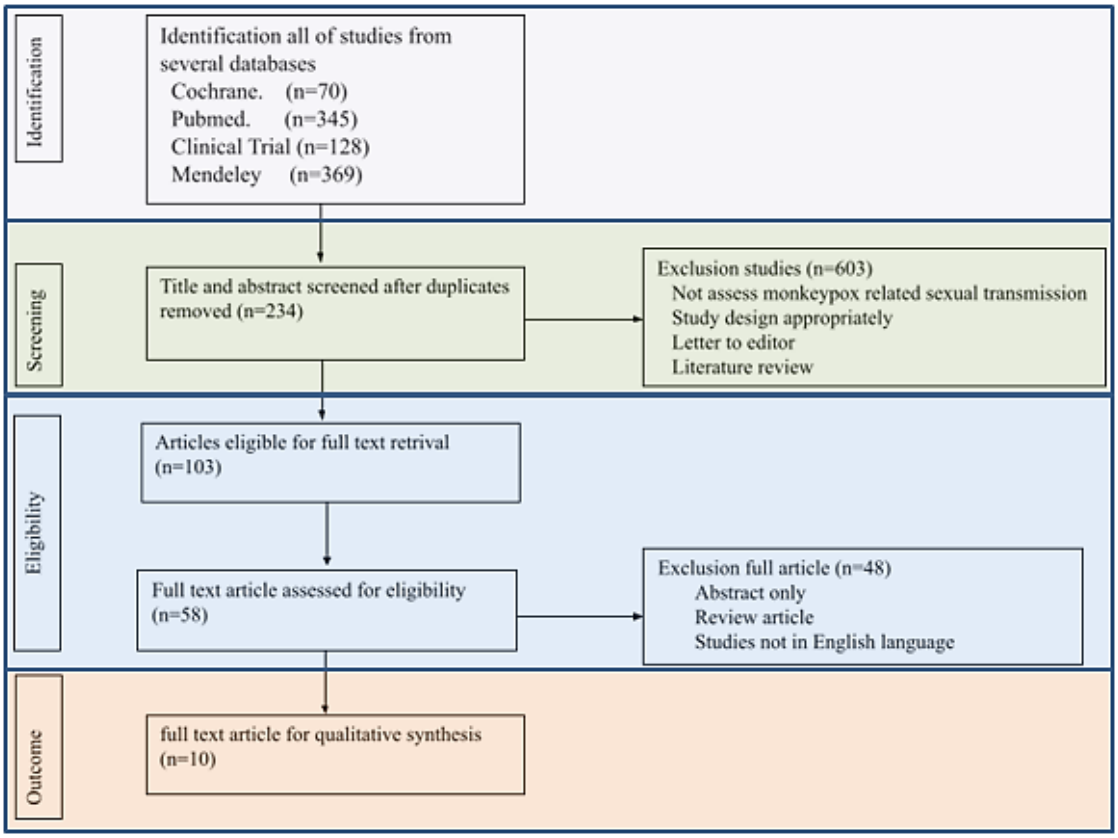

Figure 1 Prisma flow diagram.

Selection criteria

The selection criteria for this study included all relevant publications that assessed monkeypox transmission among homosexual and bisexual populations. The selected publications encompassed various study designs such as case reports, case series, prospective and retrospective cohort studies, case-control studies, and clinical trials. On the other hand, studies that did not report on monkeypox or were review articles, meta-analyses, epidemiological studies, abstracts only, non-English manuscripts, or editorials were excluded.

Data extraction

Data extraction and quality assessment were conducted by three independent authors (LA, RA, and MT) using a standardized extraction form consisting of two tables. **Table 1** focused on the characteristics of included studies, including authors and year of publication, study design, country, mean age, gender, history of smallpox vaccine, systemic signs related to lesion appearance, signs and symptoms, skin lesions, location of skin lesions, diagnostic tests, and complications. **Table 2** specifically addressed the characteristics of sexual transmission, including transmission routes, types of sexual transmission, history of sexually transmitted infections (STIs), comorbidities, symptoms related to sexual contact, treatment, and outcomes.

Bias analysis

The analysis of bias revealed that all the journals included in the study clearly outlined the population, intervention, comparison, and outcome measures. The majority of the journals

consisted of case series, followed by case reports, as the original study was not found for this research. Among the included journals, two had biases related to participant data, one had intervention bias, one had missing data bias, and one had reporting bias. Overall, all the studies assessed in this research had a low score indicating a low risk of bias.

Result

Study selection **Figure 1** provides an outline of the study selection process. The initial search across multiple databases yielded a total of 912 articles, which reduced to 234 potentially relevant articles after removing duplicates. After reviewing the titles and abstracts, 603 articles were excluded as they did not meet the eligibility criteria. Eventually, after a thorough reading of the full-text articles, 10 studies were identified that met the inclusion criteria. There were no disagreements during the study selection process. The bias analysis for all these journals is presented in **Table 1**.

Characteristics of included studies Derived from **Table 1**, 10 included studies regarding sexual transmission of re-outbreak of monkeypox diseases in 2022. All of the studies consisted of 7 case series and 3 case reports. Most of these cases were derived from Europe and the US and only 2 studies were reported from Australia and South Korea. In conclusion, a total of 1310 patients were included in this study with 99.54% being male, with a mean age of 30s years old ranging from 30-40 years old, and only 54 patients (4.12%) with a history of smallpox vaccine.

By the characteristics of the monkeypox disease in 2022, the incubation period among the patients in this study is diverse, ranging from 2 days to 21 days. There were three studies out of a total of five studies stated that most skin

Table 1 ROBINS-I analysis.

Study	*Confounding Bias*	*Participants Bias*	*Intervention Bias*	*Missing Data Bias*	*Outcome Bias*	*Reporting Bias*	*Overall Risk Bias*
Antinori et al, 2022	No	No	No	NI	No	No	Low
Girometti et al, 2022	No	No	Yes	NI	No	Yes	Low
Hammerschlang et al, 2022	No	No	No	NI	No	No	Low
Irith et al, 2022	No	Yes	No	NI	No	No	Low
Jang et al, 2022	No	No	No	NI	No	No	Low
Martinez et al, 2022	No	No	No	Yes	No	No	Low
Mestres et al, 2022	No	No	No	NI	No	No	Low
Patel et al, 2022	No	No	No	NI	No	No	Low
Thornhill et al, 2022	No	Yes	No	NI	No	No	Low
Ortiz-Martinez et al, 2022	No	No	No	NI	No	No	Low

Table 2 Characteristics included studies.

No	*Author, year of publication*	*Study design*	*Country*	*Age (Mean)*	*Gender*	*History of smallpox vaccine*	*Systemic sign to lesion appearance*	*Sign and symptom*	*Skin lesion*	*Location of skin lesion*	*Diagnostic test*	*Complication*
1.	Antinori et al, 2022. [6]	Case series	Italy	30s years old	4 Male	1 patient	1-3 days	Fever, myalgia , lymphadenopathy inguinal	Papules secreting serous, with a central umbilication	Anal, genital, thoraks, and legs	PCR (+) (patients/all patients) on skin (3/4), genital and rectal lesions(4/4), serum (1/4), plasma (1/4), seminal fluid (3/4), faeces (2/4), scab (2/4), saliva (1/4), and nasopharynx (3/4)	Bacterial infection
2.	Girometti et al, 2022.[7]	Case series	United Kindom	41 years old	54 Male	N/A	N/A	Fever, myalgia, Lymphadenopathy, fatigue, asthenia, sore throat, pruritus, no systemic symptoms	Pathognomonic skin lesions: pustular papules with a central umbilicated dip, fluid-filled vesicles, ulcerations, eschars or rash, lymphadenopathy	Penile, perianal, face, and neck, limbs, oropharynx, torso, only 1-3 anatomical sites	PCR (+) on swab on lesions, blood, urine, no specified details	Cellulitis
3.	Hammerschlang et al, 2022.[8]	Case report	Australia	30s yearsold	1 Male	N/A	Systemic sign 3 days after skin lesions	Fever, malaise, genital pain	Pustules, pruritus, rash,crust	Penile, trunk, face, limbs	PCR (+) on swab on lesions, nasaland throat	Cellulitis
5	Jang et al, 2022.[11]	Case report	South Korea	34 years old	1 male	N/A	Systemic sign 2 days after skin lesions	Fever, sore throat	Erosions covered with crusts, papules, painless ulcers with central umbilications, lymphadenopathy, maculopapular rash	Face, back, lower abdomen, penile shaft, extremities	PCR (+) (patients/all patients) on swab on lesions, nasopharynx, oropharynx (508/508)	NA
6	Martinez et al, 2022.[12]	Case series	Spain	35 years old	503 male and 5 female	N/A	N/A	Fever, myalgia, lymphadenopathy, asthenia, headache	Exanthema	Anogenital 359 patients (72.1%), legs and or arms 222 patients (44.6%), face 177 patients (35.5%), chest or abdomen 159 patients (31.9%), Back 132 patients (26.5%), palms and/or plants 124 patients (24.9%)	PCR (+) on swab on lesions	NA
7	Mestres et al, 2022.[13]	Case series	Spain	38.5 years old	12 male	4 patients of 7 patients	N/A	Fever, myalgia, fatigue, headache, malaise, proctitis, odynophagia	Pustules, genital ulcers	Genitals 111 patients (56.3%), perianal 82 patients (41.6%)	PCR (+)(patients/ all patients) on saliva (12/12), rectal swab (11/12), semen (7/9), urine	NA

No	*Author, year of publication*	*Study design*	*Country*	*Age (Mean)*	*Gender*	*History of smallpox vaccine*	*Systemic sign to lesion appearance*	*Sign and symptom*	*Skin lesion*	*Location of skin lesion*	*Diagnostic test*	*Complication*
											(9/12), faecal (8/12), nasopharynge al swab (10/12) .	
8	Patel et al, 2022.[14]	Case series	UK	38 years old	197 male	N.A	Systemic sign preceded skin lesions 102 patients, 64 patients no systemic sign	Fever, myalgia, lymphadenopathy, , fatigue, headache, arthralgia, back pain, rectal pain	Macules, papules, pustules, vesicles, scab, umbilication	Face 71 patients (36%), Trunk 70 (35.5%), Arms/legs (74%), Hands/Feet 56 patients (28.4%), genitals 111 (56.4%), Anus or perianal 82 patients (41.6%), Oropharynge al 27 (13.7%)	PCR (+) (patients/ all patients) on swab on lesions (197/197)	Secondary bacterial infection, perforated rectum due to abcess
9	Thornhill et al, 2022.[9]	Case series	Mostly in Europe and US	38. years old	527 male 1 trans	49 patients	Systemic sign preceding rash, N/A time frame	Fever, myalgia, lymphadenopathy, headache, pharyngitis, lethargy, proctitis/anorectal pain, low mood,	Vesiculopustular 291/500 (58%), macular 19/500 (4%), single ulcer 54/500(11%), multiple ulcer 95/500(19%), other 41/500 (8%) , no rash 28 (5.3%)	Anogenital, face, trunk or limbs, palms or soles	PCR (+) blood 35 patients (7%) lesion swabs 512 patients (97%), nose/ throat swab 138 patients (26%), urine 14 patients (3%), semen 29 patients (5%)	Epiglottitis, myocarditis, soft-tissue bacterial superinfection , acute kidney injury
10	Ortiz-Martinez et al, 2022.[15]	Case report lymphad enopath y, sore throat, bilateral	US	36 years 1 male old	None	NA	Cervical and inguinal	tonsillar enlargement, oropharyngeal erythema, no fever				

Table 3 Characteristics of sexual transmission.

No.	*Author, year of publication*	*Transmission*	*Sexual Orientation*	*History of STI*	*Comorbid*	*Sexual contact to symptom appearance (incubation period)*	*Treatment*	*Outcome*
1.	Antinori et al, 2022.	Sexual intercourse	Homosexual (active sexual)	Syphillis	Hepatitis B,C	N/A	Oral antivirals and oral antibiotics	Resolution in 2 weeks after the medication received
2.	Girometti et al, 2022.	Sexual intercourse	Homosexual (active sexual) 52 patients (96,3%), bisexual 2 patients (3,7%)	HSV infection 1 patient (1,85%), gonococca / chlamydial l infection 13 patients (24%)	HIV 13 patient (24%), 11 patients undetected viral load within 90 days, 2 patients between viral loads 200-500 copies per ml	Median 2 days	antibiotics 3 patients (5.7%), antibiotics and antiviral 1 patients (1.8%)	Skin eruptions cleared in maximum 3 days, median discharged from hospital 7 days
3.	Hammerschlang et al, 2022	Sexual intercourse	Homosexual (active sexual)	N/A	HIV CD4+ T Cell count >700 cells /mm3, consume abacavir, lamivudine, dolutegravir	5 days	Intramuscular antibitotic (ceftriaxone) and oral antibiotic (doxycycline)	Discharged in 13 days, not yet resolved
4.	Irith et al, 2022.	Sexual intercourse	Homosexual and bisexual (active)	Multiple STI history	Controlled HIV	NA	N/A	RT-PCR on Day 21, 24, and 37 days after diagnosis (-)
5.	Jang et al, 2022.	Sexual intercourse	Bisexual, denied sexual intercourse	None	None	No sexual contact, 21 days from initial contact	N/A	N/A
6.	Martinez et al, 2022.	Primary case, Sexual intercourse, close contact		N/A	HIV 225 patients (44.3%) Pre-exposure prophylaxis 56 patients (11%)	21 days	N/A	N/A
7.	Mestres et al, 2022.	Sexual intercourse	Homosexual (active sexual)	Syphillis 2 patients (16,6%), Chlamydia 1rachomatis + Neiserria gonorrhae 1 patients (8.3%)	HIV 4 patients (33.3%) all with undetectable HIV viral load, CD4+ T-cell counts between 400 and 860 cells/uL	N/A	N/A	N/A
8.	Patel et al, 2022.	Sexual intercourse	Homosexual (active sexual) 196 patients (99.5%)	STI history 56 patients (31.5%)	HIV 70/195 patients (35.9%) viral load <200 copies/ml 55/70 (78.6%)	Within 21 days	Antiretroviral for HIV 64/70 patients (91.4%), Antibiotic for proctitis (IV Ceftriaxone and Metronidazole)	N/A
9.	Thornhill et al, 2022.	Sexual close contact 504 patients (95%), Non Sexual Close-contact 4 patients (1%), Others 17 patients (3%), Houshold contact 3 patients (1%)	Homosexual (active sexual) 509 patients (96%) Heterosexual (active sexual) 9 patients (2%), Bisexual 10 patients (2%)	Gonorrhea 32/377 (8%), Chlamydia 20/377(5%), Syphillis 33/377(9%), HSV infection 3/377(1%), Lymphogranuloma venereum 2/377 (1%), Chlamydia +gonorrheae 5/377(1%), others 14/377(4%)	HIV 218 patients (41%) median CD4 cell count of 680 cells/mm3 . Pre-exposure prophylaxis 176/310 patients (57% of HIV Cases), Hepatitis B 6 patients (1%), Hepatitis C Ab + (8 patients (2%), Hepatitis C RNA + 49 patients (9%)	Median 7 days (range 3-20 days) out of 23 clear history	Antiretroviral for HIV including Cidofovir (2%) and Tecovirimat (2%); Vaccinia immune globulin (<1%).	N/A
10	Ortiz-Martinez et al, 2022.	Sexual contact	Homosexual or bisexual (active sexually)	Chlamydia trachomatis infection and syphillis	Pre-exposure prophylaxis (tenofovir disoproxil/emtricitabine)	7 days	Doxycycline, Amoxicillin/clavulanate 875/125 mg	20 days

lesions appeared before prodromal signs such as fever, lymphadenopathy, myalgia, and fatigue; only a few studies (2 studies) stated that prodromal signs appeared in the first 1-3 days before skin lesion appeared. The common skin lesion characteristic was vesiculopustular and ulcers with central umbilication, then the lesion became a scab two weeks after the first skin lesion, followed by lymphadenopathy inguinal. The localization of skin lesions is mainly in the anal and anogenital area, with the number of skin lesions being only a few or one lesion. Interestingly, the diagnostic test reported that PCR (+) in seminal fluids was commonly used in MSM patients. The complications mainly were cellulitis and bacterial infection.

Characteristic of sexual transmission

Regarding sexual transmission, ten studies were included, of which 80% were transmitted by sexual intercourse and in the homosexual group (MSM/ Men who have sex with Men). Only 10-20% of cases are reported in the heterosexual group. Approximately 535 patients (40.84%) had HIV as a comorbid disease, 202 patients (15.42%) had concurrent or history of Sexually Transmitted Infections (STIs), including syphilis in 44 patients (3.36%), *Chlamydia trachomatis* infection in 42 patients (3.21%), *Neisseria gonorrhoeae* infection in 73 (5.58%), *Herpes simplex virus* infection in 15 patients (1.14%), Lymphogranuloma venerum in 2 patients (0.15%), coninfection of *Chlamydia trachomatis* and syphilis in 1 patients (0,08%), coninfection of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infection in 8 patients (0.61%), and other not specified STI in 17 patients (1.30%). Another comorbid that was found in this study is Hepatitis B and C infection. The skin lesion duration appeared 5-21 days after sex without prodromal signs. The skin lesion was cured in 2-3 weeks after receiving the medication, such as oral antiviral, oral and topical antibiotic, and other additional medicine related to their comorbid disease.

Discussion

This systematic review provides a comprehensive overview to further compare the evolution of the monkeypox from data regarding the most recent 2022 outbreak. By using a structured format, we present several key points that were found in the recent outbreak, that may be used to foster diagnostic capabilities, and reveal the novel nature of the virus with focus on sexual transmission and evolution of the lesions found in the newer cases presented in **Table 4**.

Table 4 Difference in features of previous monkeypox vs monkeypox in 2022.

Comparison	*Previous Monkeypox Outbreak*	*Monkeypox Outbreak in 2022*
Epidemiology	Mainly in Africa	Europe, US, and Asia (global outbreak)
Onset	7-17 days	3-17 days
Prodromal sign to skin lesion appeared	1-3 days	Novel presentation of systemic sign appear after skin lesion on 2 male cases.[8,11]
Type of lesion	Consists of 3 stages: 1. Papular rash 2. Vesiculation and postulation 3. Crusting	Consists of 4 stages: 1. Macular/papular/vesicular 2. Pustular with umbilication 3. Scabbing over 4. Desquamation
Location of lesion	Usually found on face, chest, and upper and lower extremities	Can be found on every part of body, particularly on hands and genital area
Transmission	Animal-to-human Eating inadequately cooked meat and other animal products of infected animals	Human-to-human Direct contact with monkeypox rash, scabs, or body fluids, respiratory secretions.
Sexual transmission	Not mentioned	During sexual contact/intercourse In homosexual group (MSM/ Men Sex with Men) In diagnostic test, PCR (+) in seminal fluid

Sexual transmission in 2022 monkeypox In contrast with the previous local outbreak, we found that these multinational outbreaks were more likely to infect males, with a 99.54% predominance. These findings may be related to the incapability of blood-testis barriers in filtering out viruses, especially where there was also systemic and local inflammation present. This may cause viral shedding in the male reproductive tract, causing virus findings in semen, with or without close sexual contact as a mode of transmission.[7] In this study among all known data, we found 36 seminal fluid samples which tested positive for MPX Virus, however, it is still unclear whether the positive seminal fluid samples were caused by sexual contact transmission or through the usual route of transmission. Although a clear conclusion was not able to be drawn, this study found that 80% of suspected transmissions in the cases described are caused through sexual contact, a finding that is contradictory to classical cases of monkeypox. This suspicion regarding the novel sexual transmission is based on the mounting amount of genital and perianal lesions which suggest that transmission may have happened through local inoculation through mucosal as well as skin-to-skin contact during sexual intercourse. These are distinctive natures that haven't been reported on past outbreak episodes.[7,16]

These findings are also backed by data that shows approximately 15.42% of the cases had an elevated rate of concurrent Sexually Transmitted Infections (STIs), including syphilis, gonorrhea, herpes simplex infection, and HIV. These findings indicate that unhealthy sexual behaviors may have a pivotal role in virus spread, including unprotected intercourse and multiple sex partners.[8]

Another prominent finding of this study shows that of the suspected sexual contact cases, all of them occurred among homosexuals, with a little portion of bisexuals. This may be linked with the comorbidity of HIV-status that immunocompromised individuals such as HIV-patients are said to possess higher risk in contracting monkeypox. However, HIV status as a risk factor for Monkeypox disease is still debatable, studies have reported 40.84% (535 cases) from a total of 1.039 reported patients were HIV-positive, with ongoing medication and varying HIV viral loads and CD4+ T Cell count status.[8] However, some literatures postulate that untreated and uncontrolled HIV infections may increase the severity and duration of clinical courses.[7,8,11] Other comorbidities found in this study include Hepatitis B and C infection. The presence of the infection, however, may be attributed to the HIV positivity rate, as Hepatitis B and C may be HIV-related co-infection because of their similarity in route of infection as well as the risk of infection, including injected drug use, sexual contact, and mother to child transmission.[12] No potential link between the two diseases and monkeypox were found in literature, hence implying the coincidental nature of the diseases.

The newer features of monkeypox in 2022 Another relevant key point that contrasts between the current and previous outbreak is the median age of patients. In the 1970s, the median age of patients was 4, which increased to 10 in 2000 to 2009 data, and 21 in 2010 to 2019 data.[13] The current multinational outbreak is commonly present in adults with a mean age of 30. This finding further supports the hypothesis of human-to-human transmission, specifically through sexual contact during the current outbreak. This phenomenon is also consistent with a previous study by Bunge, et al (2022) that observed that following the 1980 eradication of smallpox, routine vaccination was no longer carried out. Only adults aged above 40-45 years old had a previous history of routine smallpox vaccination, causing the younger population to

be at risk. (Peiró-Mestres et al.) This evidence supported the role of smallpox vaccination in preventing the disease. Among all samples derived from this study, only 54 (4.12%) samples had a recorded history of the smallpox vaccine. However, no further details were explained about the vaccination, as immunity protection through vaccination will wane through the years, relationship between vaccine protection and monkeypox is difficult to establish.

The incubation period among the patients in this study is diverse, ranging from 2 days to 21 days, similar to the mean 12 days (range 5-24 days) incubation period from literature. However, the result from this study may be biased, as a guideline from the Centers for Disease Control and Prevention (CDC) states that monitoring should be carried out until 21 days after exposure to a potential source of infection. As a result, most studies do not specify the precise incubation period, only providing an incubation range of "within 21 days from initial exposure", thus hindering us from making any conclusions regarding the incubation period.[12,9]

Classic monkeypox cases presented with biphasic clinical course features. Miscellaneous findings on the clinical course of the disease began from the presentation of the newest outbreaks. The prodromal phase may precede rash with fever, malaise, sweats, lymphadenopathy, and headache, then after 2-4 days followed by the appearance of skin lesions. In addition, this study found that among the reported 151 patients (who experienced systemic signs before the appearance of skin lesions without a specific timeframe) 1 patient had skin lesions between the 1st to 3rd days after systemic signs occurred, and 64 patients had no systemic signs. These findings are contradictory with past literature which states that systemic signs usually occur before rash development.[12] From these ten studies, we found that the skin lesions were vesiculopustular and ulcers with central umbilication and then became scabs in 2 weeks after the first skin lesions. The evolution of these skin lesions is a characteristics of the 2022 monkeypox outbreak, also known as the "four stages of monkeypox lesions".[12] In addition, The localization of skin lesions was largely found in the anal and anogenital areas with a total of 631 patients (60.7%) all patients homosexual and bisexual. Meanwhile, in the male population, 57 cases were reported of penile shaft lesions that are umbilicated with central scabbing, pustule, macule, and erythematous penile skin. The lesions resemble lymphadenopathy inguinal which is very painful and it is common 7 in those with a previous history of sexual activity and intimate contact.[9]

Although treatment guidelines for monkeypox disease have not yet been established through observing 10 studies with various reported symptoms, we conclude that clinicians provided supportive medications specifically indicated by the patient's symptoms. While the main focus of therapy were comorbidities like STI and HIV. Antiretrovirals are given to monkeypox patients with HIV.[14] The majority of patients were given oral antibiotics to cure secondary infections of the lesions.[6,7,8,14] Overall 10 studies reported genuine outcome resolution within 7 to 21 days.

Looking at all of the data present in this systematic review, we provides supportive data emphasizing the role of sexual transmission in the novel nature of this disease. However, the inclusion of the monkeypox disease as an STD still requires further investigation and elaboration as the current data presented cases that were mostly among men. Further investigation and data collection on the wider population is necessary to establish sexual transmission that is not only among men but also among women.

In general, STIs are primarily spread through sexual contact, whether oral, vaginal, or anal. Whereas before the findings of current novel presentations, monkeypox transmission was limited to direct contact, with no records of sexual transmission. The findings in this study may provide primary epidemiological evidence of possible sexual transmission in newer cases. To further establish this disease as an STD, we encourage, other more broad studies focusing on the possibility of this disease as an STD both in men and women.

Limitation

This review is not without its limitations. Firstly, this study mainly consists of case reports and case series with low levels of evidence; Further research with big-scale criteria is needed to describe more detailed and verified data. Secondly, Most cases have incomplete data, and additional essential data may have been missed. Thirdly, although more than half of the studies included have presented data on the transmission of monkeypox through sexual contact, there are still many studies that do not claim monkeypox as a disease caused by sexually transmitted infection. Therefore, an in-depth analysis of this is required.

Conclusion

The homosexual and bisexual populations were the most high-risk population in the 2022 outbreak of monkeypox disease because of their habitual sexual activity and its related comorbidities. Overall, we found significant data as evidence of the sexually transmitted infection in monkeypox virus. The findings in this review may supplement information to further establish clinical guidelines on the new presentation of monkeypox disease. This review also provides data on special populations, which may be used to improve prevention in regards to the sexual mode of transmission. Further large-scale studies are necessary to describe the data in more detail and verify with stronger evidence.

References

1. Alakunle E, Moens U, Nchinda G, Okeke MI. Monkeypox Virus in Nigeria: Infection Biology, Epidemiology, and Evolution. *Viruses*. 2020;**12(11)**:1257. doi: 10.3390/v12111257..
2. Vaughan A, Aarons E, Astbury J. Two cases of monkeypox imported to the United Kingdom, September 2018. Eurosurveillance [Internet]. 2018 Sep 9 [cited 2022 Aug 18]; Available from: /pmc/articles/PMC6157091/
3. Taylor L. Monkeypox: WHO declares a public health emergency of international concern. *BMJ*. 2022:**378**:o1874. doi: 10.1136/bmj.o1874.
4. The Indonesian Ministry of Health. Kasus Monkepox Pertama di Indonesia Terkonfirmasi [Internet]. Sehat Negeriku. [cited 2022 Sep 8]. Available from: URL: https://sehatnegeriku.kemkes.go.id/baca/rilis-media/20220820/3140968/kasus-monkeypox-p ertama-di-indonesia-terkonfirmasi-2/
5. Moore J, Rathish B, Zahra F. Monkeypox. StatPearls. 2022 Jul 16 [cited 2022 Aug 18]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK574519/
6. Antinori A, Mazzotta V, Vita S, Carletti F, Tacconi D, Lapini LE, et al. Epidemiological, clinical and virological characteristics of four cases of monkeypox support transmission through sexual contact, Italy, May 2022. Eurosurveillance [Internet]. 2022 Jun 2 [cited 2022 Aug 14];27(22).Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2022.27.22.2200421
7. Girometti N, Byrne R, Bracchi M, Heskin J, McOwan A, Tittle V, et al. Demographic and clinical characteristics of confirmed human monkeypox virus cases in individuals attending a sexual health centre in London, UK: an observational analysis. Lancet Infect Dis [Internet]. 2022 Jul [cited 2022 Aug 14];S147330992200411X. Available from:

https://linkinghub.elsevier.com/retrieve/pii/S147330992200411X

8. Hammerschlag Y, MacLeod G, Papadakis G, Adan Sanchez A, Druce J, Taiaroa G, et al. Monkeypox infection presenting as genital rash, Australia, May 2022. Eurosurveillance [Internet]. 2022 Jun 2 [cited 2022 Aug 14];27(22). Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2022.27.22.2200411
9. Thornhill JP, Barkati S, Walmsley S, Rockstroh J, Antinori A, Harrison LB, et al. Monkeypox Virus Infection in Humans across 16 Countries — April–June 2022. N Engl J Med [Internet]. 2022 Jul 21 [cited 2022 Aug 14];NEJMoa2207323. Available from: http://www.nejm.org/doi/10.1056/NEJMoa2207323
10. Irith D, Christophe V, Kenyon C, Coppens J, Dorien V, Hilde S, et al. Asymptomatic monkeypox virus infections among male sexual health clinic attendees in Belgium. 2022.
11. Jang YR, Lee M, Shin H, Kim JW, Choi M min, Kim YM, et al. The First Case of Monkeypox in the Republic of Korea. *J Korean Med Sci* [Internet]. 2022 [cited 2022 Aug 14];**37(27)**:e224. Available from: https://jkms.org/DOIx.php?id=10.3346/jkms.2022.37.e224
12. Iñigo Martínez J, Gil Montalbán E, Jiménez Bueno S, Martín Martínez F, Nieto Juliá A, Sánchez Díaz J, et al. Monkeypox outbreak predominantly affecting men who have sex with men, Madrid, Spain, 26 April to 16 June 2022. Eurosurveillance [Internet]. 2022 Jul 7 [cited 2022 Aug 14];27(27). Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2022.27.27.2200471
13. Peiró-Mestres A, Fuertes I, Camprubí-Ferrer D, Marcos MÁ, Vilella A, Navarro M, et al. Frequent detection of monkeypox virus DNA in saliva, semen, and other clinical samples from 12 patients, Barcelona, Spain, May to June 2022. Eurosurveillance [Internet]. 2022 Jul [cited 2022 Aug14];27(28). Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2022.27.28.2200503
14. Patel A, Bilinska J, Tam JCH, Da Silva Fontoura D, Mason CY, Daunt A, et al. Clinical features and novel presentations of human monkeypox in a central London centre during the 2022 outbreak: descriptive case series. BMJ [Internet]. 2022 Jul 28 [cited 2022 Aug 14];e072410. Available from: https://www.bmj.com/lookup/doi/10.1136/bmj-2022-072410
15. Ortiz-Martínez Y, Rodríguez-Morales AJ, Franco-Paredes C, Chastain DB, Gharamti AA, Vargas Barahona L, et al. Monkeypox – a description of the clinical progression of skin lesions: a case report from Colorado, USA. Ther Adv Infect Dis [Internet]. 2022 Jan [cited 2022 Aug 14];9:204993612211177. Available from: http://journals.sagepub.com/doi/10.1177/20499361221117726
16. De Baetselier I, Van Dijck C, Kenyon C, Coppens J, Michiels J, de Block T, et al. Retrospective detection of asymptomatic monkeypox virus infections among male sexual health clinic attendees in Belgium. Nat Med. 2022.