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Sexually transmitted diseases and HIV co-infection among adult male patients in the 2022 monkeypox outbreak: a systematic review and meta-analysis

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Abstract

Aim. This meta-analysis estimates the prevalence of sexually transmitted diseases (STIs) and HIV infection among male patients diagnosed with Monkeypox during the 2022 outbreak. The study also explores contextual factors associated with higher risk of monkeypox infection. Methods. A systematic review of literature was initially conducted through PubMed/ Medline, Scopus, and Google Scholar to retrieve observational studies describing demographics and medical characteristics of Monkeypox patients affected in the 2022 outbreak. The System for the Unified Management, Assessment, and Review of Information -Joanna Briggs Institute (SUMARI JBI) guidelines was used to conduct the meta-analysis of this review. All data relevant to prevalence of HIV and STIs in male patients diagnosed with Monkeypox were extracted and exported into the JBI SUMARI. To assess point prevalence of HIV and STIs, we used the Freeman-Tukey-type arcsine square root transformation to stabilize the variances of the raw proportions. All estimates were weighted and pooled by the inverse variance using a fixed-effects model. We then used a random model to account for sampling variation and reported heterogeneity in effect size noted across studies in the fixed-effect model. The I^2 test statistic and P values were used to measure the heterogeneity between studies. Values of I^2 test statistic results were interpreted as follows: low (25%), moderate (50%) and high (75%). Results. Six studies from Spain and the UK met the inclusion criteria. These studies described a total of 541 male patients with monkeypox, 214 of them were positive for HIV and 255 had other STIs. Overall estimated prevalence of HIV and STIs was 40% (95% CI = 0.31%, 0.50%; $\chi^2 = 15$) and 43% (95% CI = 25%, 61%; $\chi^2 = 118$), respectively. Outcomes indicated moderate to high heterogeneity in the overall analyses. Conclusions. Approximately four in ten male patients affected in the 2022 Monkeypox outbreak had HIV and/or other STIs. Necessary public health measures should target male and female patients who are at risk of Monkeypox infection to prevent the transmission of serious infections such as HIV and other STIs.

Introduction

The twenty first century has witnessed the emergence and re-emergence of several zoonotic viral infections such as severe acute respiratory syndrome, Middle East respiratory syndrome, and more lately corona virus disease-2019 (COVID-19) [1]. As the world was recovering from the repercussions of COVID-19, a newly emerging zoonotic viral infection had been identified in the form of Monkeypox. Originally identified in monkeys and other animals, some cases were reported among humans, however, they did not attract much attention due to the zoonotic nature of this disease and the low numbers of human cases. Most cases of Monkeypox occurred in Africa with some sporadic cases occurring elsewhere. However, a noticeable surge of cases was reported in May 2022

in countries not previously known to report such infection such as Europe and North America [2]. As of 4 September 2023, there were 89,752 confirmed cases and 157 confirmed deaths related to this disease [3]. It is primarily manifested as self-limiting skin lesions, however, other clinical manifestations were described in a recent systematic review which included observational studies conducted during the twenty first century and these were fever, lymphadenopathy, fatigue, sore throat and headache [4]. Despite the self-limiting nature in most cases, other disease outcomes could present in the form of severe complications such as encephalitis, pneumonia, gastrointestinal symptoms, secondary bacterial skin infection, and eye problems in the form of keratitis, blurred vision, and corneal scarring [5].The infection is transmissible from animals to humans, and it can be transmitted among humans through multiple routes. This is well-represented by the 2022 outbreak which affected large numbers of humans in a total of 114 countries, 107 of them have not historically reported monkeypox [6]. Social activities that involved skin-to-skin contact, contact with fomites such as bed linens, and exposure to respiratory droplets were highlighted as the main predisposing factors in this outbreak [7]. Among these social activities, sexual intercourse among men who have sex with men (MSM), stands out as the most likely risky behavior in predisposing to this infection [8]. Patients were primarily seen in sexual healthcare facilities complaining of genital lesions, which prompted concerned authorities to look into the possibility of considering Monkeypox as an emerging STI [2]. A striking feature of the 2022 outbreak was the presence of comorbidities in the form of STIs and HIV in the affected patients. Another feature was the involvement of sexual networks whereby patients had reported multiple sexual partners (homosexual and bisexual). Considerably lower numbers of female patients were affected and these reported previous contact with males in a sexual or household context [2]. Despite the low numbers of infected women, vulnerable populations of pregnant women, breastfeeding mothers and even children were under the spotlight as potentially susceptible patients [9].

Previous studies in Africa identified people with uncontrolled HIV to have worse outcomes, including more extensive and longer-lasting lesions, more complications, and several deaths [10]. On the other hand, MSM are considered a high-risk group for STIs [11]. It is important at this stage to assess potential risk factors and identify risk groups susceptible to monkeypox. This will facilitate designing the appropriate preventive measures that target susceptible populations

Despite the wide distribution of monkeypox in the current outbreak that involved 114 countries up to date [12], Europe and the Americas represent the most highly affected geographic areas. The outbreak initially was identified in the UK and later in Spain and hence many studies were conducted in these two countries during the first months of the outbreak. Therefore we conducted this meta-analysis to estimate the prevalence of STIs and HIV infection among adult male patients reported in

Spain and the UK considering their epidemiological importance in the initiation and spread of the infection.

Materials and Methods

Eligibility criteria

Studies were considered eligible for inclusion in this review if they had the following criteria.

1. Studies on human monkeypox infections.
2. Case series, cross-sectional, cohort studies describing prevalence of STIs and HIV among monkeypox
cases in the 2022 outbreak.
3. Studies from countries/geographic regions that were initially affected by the outbreak in Europe: Spain and the UK
4. Studies published in English language.
5. Publication date: 1, January 2022 to 30, September 2022.
6. Patients: Male patients

Studies were excluded if they were.

1. Clinical trials, opinion, commentary, letter to the editor, editorial, review or case reports
2. Reporting other geographic locations

Information sources

Literature of the following databases were searched: PubMed/ Medline, Scopus, and Google Scholar. References of retrieved articles were searched where applicable. Further, the websites of the WHO, European Centre for Disease Prevention and Control (ECDC), and Centers for Disease Control and Prevention (CDC) were searched for relevant Keywords. Data search was conducted for literature published within the period: 1 January 2022 till 30 September 2022.

Search strategy

The included databases were initially searched for the keywords: “Monkeypox” and “2022”, using the following filters: Observational studies, Case Series, Cross-sectional studies, Human studies, English language, and period from 1/1/2022- 30/9/2022. The WHO website was consulted to obtain data on the most affected geographic areas by the outbreak. The retrieved articles were then searched for the following keywords: “Spain”, “UK”, and their references were also searched to ensure retrieving all relevant articles.

Selection process

Two reviewers (N. D-O. and O. A-H.) worked independently to select eligible articles. This was done by initial screening of titles and abstracts of retrieved articles. Only relevant articles were screened for full text.

Data collection process

Two reviewers (A.Raheem. J.; A.Rahman. J) independently collected data from selected articles.
All collected data were further revised by a third reviewer (A.A-H.) to confirm accuracy of retrieved data.

Data items

Collected data included: Author(s) name; Study type; Country; Number of monkeypox cases reported by the study; sociodemographic characteristics of patients including: age, sexual orientation; disease factors including: history of HIV, history of sexual transmitted diseases (STIS) (concurrent or past), and possible transmission route.

Study risk of bias assessment

Risk of bias (methodological quality) in included articles was determined using Joanna Briggs institute critical appraisal tools for case series [13], cohort studies, and cross-sectional studies [14]. Two reviewers (N. D-O. and A. A-H.) worked independently to assess all studies.

Data synthesis

A meta-analysis was considered the most appropriate approach for this study. The System for the Unified Management, Assessment, and Review of Information -Joanna Briggs Institute (SUMARI JBI) guidelines was used by author N.A. to conduct the meta-analysis of this review [15]. First, all data relevant to prevalence of HIV and STIs in male patients diagnosed with Monkeypox were extracted and exported into the JBI SUMARI.

To assess point prevalence of HIV and STIs, we used the Freeman-Tukey type arcsine square root transformation to stabilize the variances of the raw proportions. All estimates were weighted and pooled by the inverse variance using a fixed-effect model. We then used a random model to account for sampling variation and reported heterogeneity in effect size noted across studies in the fixed-effect model. The I^2 test statistic and P values were used to measure the heterogeneity between studies. A value of I^2 test statistic results of 25%, 50% and 75% was considered as low, moderate, and high respectively.

Reporting bias assessment

Missing results were related to the reported types of STIs and their prevalence among patients. This data was determined to be influenced by availability of data on screening for the STIs or the lack of retrieved past history on previous infections with STIs.

Results

Study selection

A total of six articles were determined to be appropriate for inclusion in this review. The flowchart that describes the selection process is presented in Figure 1.

Included studies and their findings

As of 30 September 2022, only six studies reported prevalence data on HIV and STIs among adult male patients with monkeypox and met all criteria for inclusion. The data for all studies were reported from two European countries (Spain and the UK) in the form of case series, cross-sectional, and cohort studies. There were three studies which enrolled male patients from Spain and another three studies from the UK (Table 1).

In these studies, enrollment was based on the presence of HIV and other STIs among patients diagnosed with monkeypox. Among the six studies of male patients diagnosed with monkeypox, the pooled prevalence of HIV was 40% (95% CI = 0.31%, 0.50%; $\chi 2 = 15$) and 43% (95% CI = 25%, 61%; $\chi 2 = 118$), for other STIs (Figures 2, 3).The I^2 test of homogeneity was highly significant ($P \leq 0.001$). Accordingly random effects estimates were used. Studies did not provide enough data to stratify prevalence based on age, race, or circumcision status, all of which can affect infection risk. Therefore, we were unable to quantify estimates of HIV and other STIs prevalence for each subgroup.

Risk of bias assessment

Only two studies were assessed as having a low (Catala et al) and a moderate (Vusirikala et al) risk of bias according to The JBI critical appraisal criteria for cross-sectional studies, and case series. Reasons behind this assessment are mentioned in Table- 2.

Discussion

One year has passed since the identification of the first batch of patients with monkeypox in the global outbreak that emerged in 2022. The outbreak is still ongoing and more countries are being affected, though the greatest majority of those countries are not historically known to be affected by this

infection. According to the most recent data reported by the WHO on August 14, 2023, an estimated 1020 new cases and three new deaths were reported during the period from 14 July-9 August 2023 with most of these cases being reported in the Western Pacific region [22]. Further, the risk for monkeypox at the global level is still assessed moderate at most parts of the world including Africa, Eastern Mediterranean region, Europe and the Americas. Sexual orientation and occurrence of specific co-morbidities in the current Monkeypox outbreak with significant public health consequences prompted the performance of this study. We focused on studies from the UK and Spain because these represented the most commonly affected two countries at the outset of the outbreak. At present, after almost one year, the UK and Spain are still among the most commonly affected ten countries worldwide [22].

Although monkeypox is not a recent disease, re-emergence of this infection drew attention due to the changing trends in epidemiology. In their systematic review published in early 2022, Bunge et al investigated the evolving epidemiology of human monkeypox in the last two decades, and highlighted the changing trends in geography (outside Africa), age (adults), and severity of disease outcomes (mortality) [23]. Authors attributed the increasing human-human transmission to cessation of smallpox vaccination and waning immunity of populations [23]. However, sexual orientation and intimate social activities were given more attention as the main risk factors in transmission in later reports [24].

This analysis described a total of 541 male patients and the associated co-morbidities of HIV and STIs. All studies reported that a substantial proportion of patients was positive for HIV. On the other hand, all studies, except one [21] reported that at least one in four patients had one or more concurrent STI. Patients were in their late thirties- early forties, mainly MSM and the sexual route represented the only confirmed route of transmission in most studies. This highlights the risk for transmission of HIV and STIs in general, and is consistent with recent surveys which highlighted the substantial proportion of STIs among monkeypox patients. Hoffmann et al (2022) described a cohort of patients in Germany in the current outbreak to be exclusively MSM; 46.7% of them had HIV and 59.0% were diagnosed with an STI during the six months-period prior to monkeypox infection [25]. Similar findings are reported from patients diagnosed in the United States where HIV prevalence was 38%, and 41% of them were diagnosed with at least one STIs in the preceding year [26].

In this review, the reported STIs were gonorrhea, chlamydia, genital herpes, syphilis and *Mycoplasma genitalium* in descending order. It is worth noting that gonorrhea reached its lowest incidence in the United States by the year 2009 [27]. Syphilis, on the other hand was on the verge of eradication by the year 2000 [28], however, since that year a steady rise of cases was noticed with severe symptoms such as neurosyphilis and ocular syphilis being noticed among MSM [29]. It is also noticeable that

as monkeypox cases were surging during May 2022, another surge in the prevalence of STIs was noticed in the post-COVID era specifically congenital syphilis, gonorrhea and syphilis [30]. The so-called “modern” resurgence of syphilis is an important public health problem in the US and other high-income countries. Of particular interest is congenital syphilis, a major cause of severe adverse pregnancy outcomes such as low birth weight, hepatomegaly, osteolytic bone lesions that may be associated with fractures, pseudoparalysis, central nervous system infection, and long-term disabilities. A recent report warned that cases of congenital syphilis have increased by 32% in the US in the years 2020- 2021, with > 2,000 cases reported in 2021 alone [31]. The public health burden of these STIs is mainly attributed to the serious adverse disease outcomes. There is also the anticipated burden of prevention and treatment outcomes on healthcare systems, which aim to integrate screening, vaccination and antimicrobial therapy in the comprehensive plan of care of patients and susceptible populations. Moreover, bacteria responsible for certain STIs are rapidly developing antibiotic resistance. It was reported recently that azithromycin resistance was more likely among MSM and among HIV patients [32]

This analysis estimated that the reported prevalence of HIV and other STIs among patients with monkeypox was high, yet the total estimates varied widely between studies. Estimates of HIV prevalence ranged from 2% in Gomez-Garberi [18] to 26.95% in Patel et al [19]. The STIs prevalence yields similar estimates which confirms the importance of demographic and clinical variables when considering patients who are at higher risk of developing monkeypox. Although we could not directly calculate the pooled prevalence of HIV and STIs in patients with certain clinical demographics, it would be reasonable to assume that risk of transmission in this population is high (40% in HIV patients and 43% in other STIs patients). The available data from earlier studies suggest that MSM subgroup is associated with a higher risk of infection. Although more data are needed to clarify the mechanism by which sexual orientation affects baseline risk of infection, based on the available data, MSM patients can be considered at higher risk of developing monkeypox than heterosexual male patients. Similar results were reported by recent studies. A recent systematic review estimated that 40.3% of monkeypox cases that were reported in epidemiological studies from 2018-2022 were HIV positive [33].

Other demographic features like age were also characteristic. In this study patients were in the late thirties or early forties. The last report of the WHO pointed out that median age of patients is 34, probably due to the inclusion of children aged 0-17 years in the total sample of patients.

At the beginning of the outbreak, the most common exposure setting was party with sexual contact, however, in the last three months the main exposure setting was party with no sexual contact, while

the household setting constituted 14% of the cases [22]. This has serious public health implications because risk of infection may extend to other commonly considered non-risk groups for the infection. This review has limitations. The high heterogeneity could be considered a major limitation, therefore clinical judgment is warranted to decide whether, in fact, we included studies that were "too different" to be included, mainly in terms of diagnostic criteria of HIV and STIs, type of studies and sample size. Second, because most of the studies about HIV did not differentiate HIV from AIDS, the estimates provided included both. The estimates of STIs included also large categories of different types of infection.

Finally, we could not calculate the prevalence rate of HIV or STIs for certain subgroups, such as circumcised patients, age groups, sexual orientation, or HIV-viral load due to limited data. This analysis, however, has several strengths. By using comprehensive search strategy and a priori inclusion/exclusion criteria, these results provide a more updated picture of monkeypox prevalence and its association with HIV and other STIs infection. Our findings show the pooled estimates have relatively narrow confidence intervals, mainly for the HIV patients and are consistent with previous epidemiologic studies.

The pooled prevalence values provided in our analysis can be used as an estimate of baseline probability in an evidence-based approach. However, more prevalence meta-analysis is needed in the future to provide healthcare professionals with baseline estimates of risk of monkeypox among certain populations.

Specific Public Health interventions have been recommended in the context of the monkeypox outbreak such as vaccination, messaging, and individual behavior modification and these may have contributed to the overall decline in cases worldwide [30]. However, more research is warranted to identify the most effective methods in preventing new cases. Further, officials are warranted to allocate sufficient funding and to adopt appropriate national strategy targeted towards sexual health promotion [29]. A comprehensive sexual health screening to conduct testing for other STI should be included for all monkeypox patients [34]. It is also encouraged that clinicians in different disciplines to be aware of the clinical features of this infection [35]. This is for two main reasons. Firstly, patients can be identified early in the disease process which will improve the disease outcomes by offering the patient the appropriate referral and treatment plan. Secondly, early identification will help prevent transmission to others which will have a great impact particularly for the sexual networks involved. Since patient education and cooperation are two main factors in prevention of disease transmission, it is also recommended to discuss safer sexual practices with at-risk groups namely MSM and engage them in planning of public health measures that could be effective in counteracting the disease.

Conclusions

Approximately four in ten male patients with Monkeypox have HIV and/or other STIs. Necessary public health programs should target male and female patients who are at risk of Monkeypox infection to prevent the transmission of serious infections such as HIV and other STIs.

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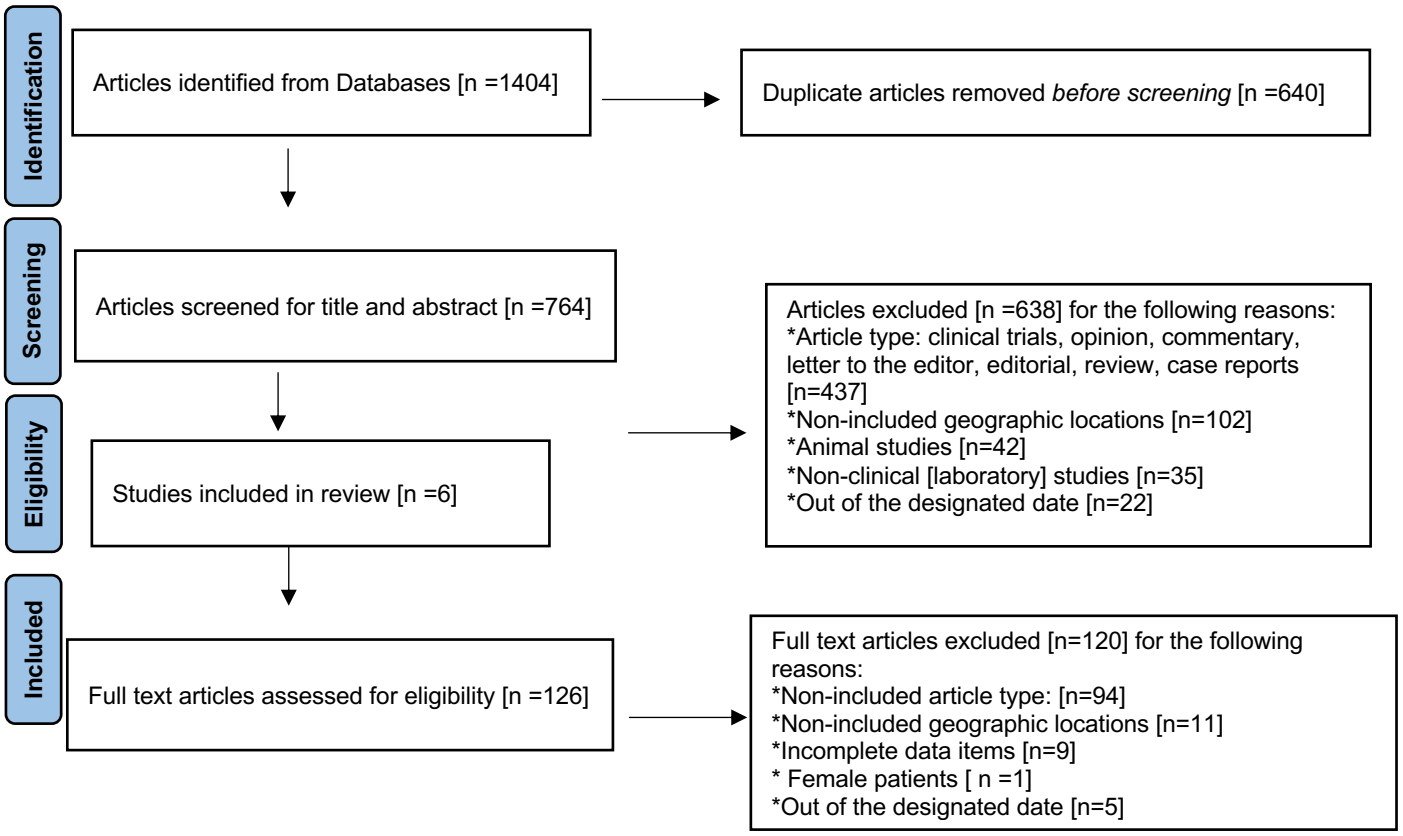

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) flowchart displaying the identification and selection process of studies retrieved via: MEDLINE/PubMed, Scopus, and Google Scholar databases.

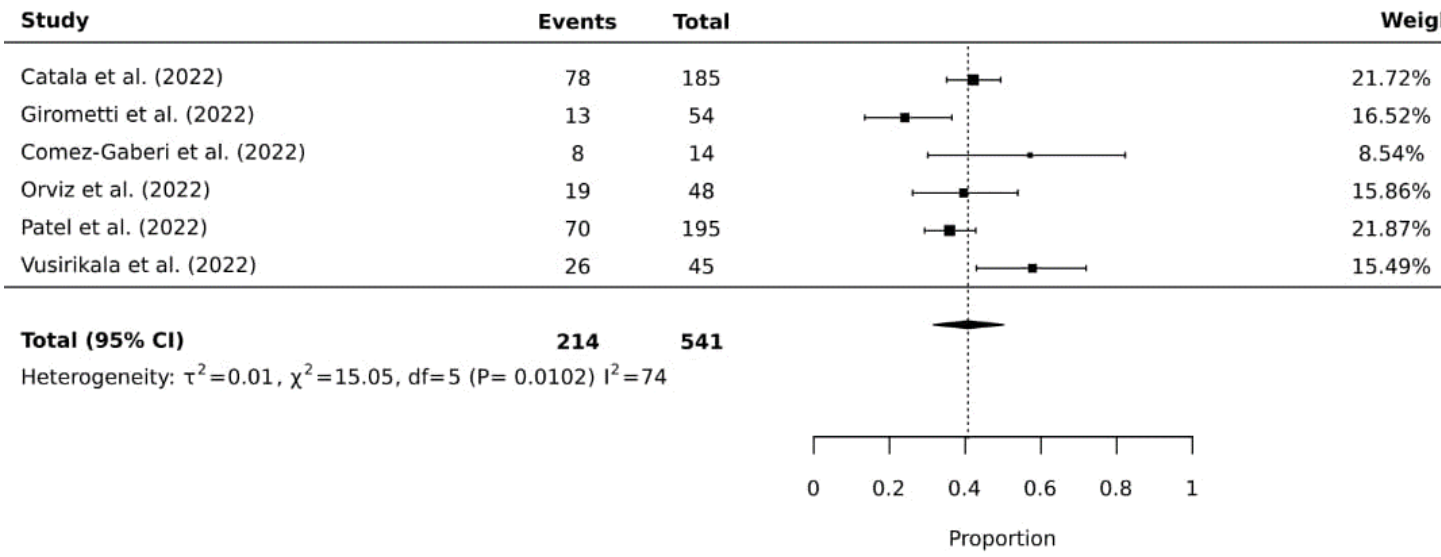

Figure 2. Meta-analysis and forest plot presentation of HIV among male patients with Monkeypox (based on studies from the UK and Spain on the 2022 outbreak).

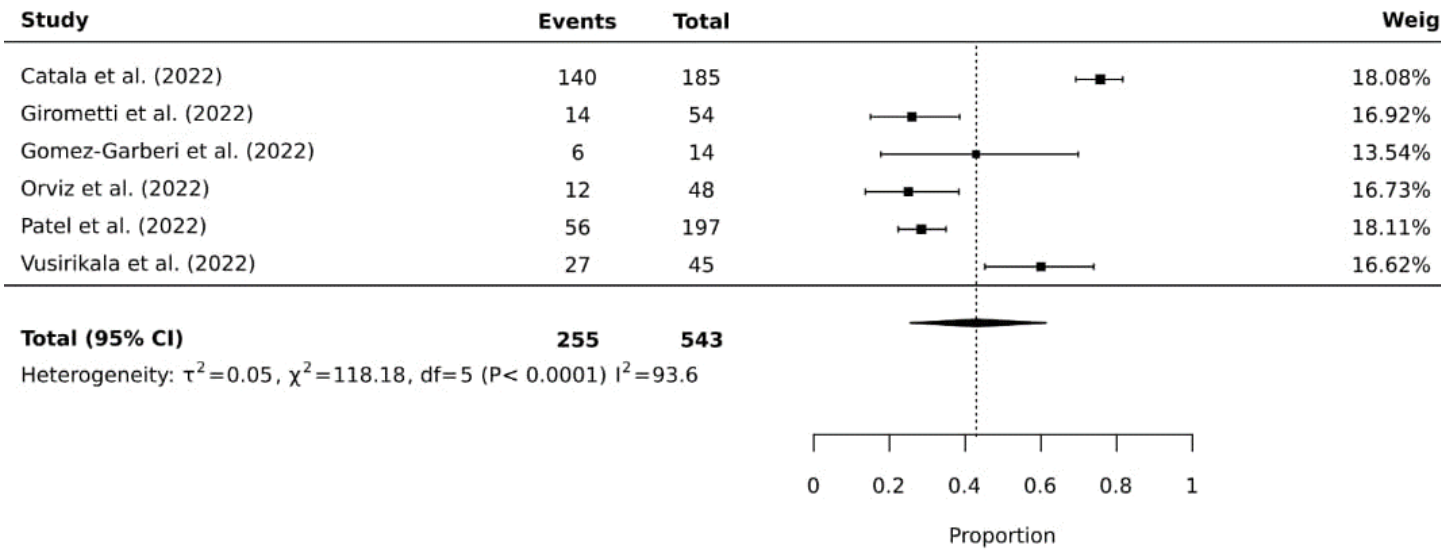

Figure 3. Meta-analysis and forest plot presentation of STIs among male patients with Monkeypox (based on studies from the UK and Spain on the 2022 outbreak).

Table 1. Sexually transmitted diseases and HIV infection among adult male Monkeypox patients affected during the 2022 outbreak in Spain and the UK. Studies were published up until 30 September 2022.

Authors	Study type	Country	Patient No	Age (years) (Mean or Median)	HIV +ve (No, %)	Other STIs (No, %)	MSM	Sexual rout of transmission
Catala et al [16]	Prospective cross-sectional	Spain	185	M= 38.7	78 (42.0%)	140 (76.0%) (concurrent)	99%	100%
Orviz et al [17]	Cross-sectional	Spain	48	Med= 35	19 (39.5%)	12 (25.0%) (Concurrent) Gonorrhea (6) Syphilis (4) Mycoplasma genitalium (1)	97.9%	100%
Gomez-Garberi et al [18]	prospective observational	Spain	14	Med=42	8 (57%)	43% Gonorrhea (1) Chlamydia (2) Syphilis (1) Mycoplasma genitalium (1) Genital herpes (1)	71%	12 (85.7%)
Patel et al [19]	Case series	UK	197	Med=38	70/195 (35.9%)	56 (31.5%) of screened patients (concurrent) Gonorrhea: 34 (21.1%) Chlamydia: 18 (11.2%) Genital herpes: 11 (7.0%) Syphilis: 6 (3.7%) > one STI: 12:	196/197 (99.5%)	170/177: (96.0%)
Girometti et al [20]	Observational	UK	54	Med= 41	13 (24%)	(25.0%) (concurrent) 13/51 (25.0%):positive Gonorrhoea (9) Chlamydia (6) Gonorrhoea & Chlamydia (2)	100%	100%
Vusirikala et al [21]	Cross-sectional	UK	45	Med= 40	26%	27 (60.0%) (past history)	44 (98.0%)	100%

M: Male; MSM: Men who have sex with men.

Table 2. Studies that showed a low -moderate risk of bias in methodological quality, and the reasons for this assessment.

Study	Level of risk	Reasons: Lack of diagnostic tests or assessment methods
Catala et al [16]	Low	1. Screening tests of concurrent STIs was not mentioned 2. Types of concurrent types of STIs were not mentioned
Vusirikala et al [21]	Moderate	1. Only past history of STIs was mentioned 2. Screening tests of concurrent STIs were not mentioned 3. Types of past and concurrent types of STIs were not mentioned