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Systematic Review

Investigation of the Effects of Previous Smallpox Vaccination against Monkeypox Disease: A Systemic Review

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Abstract

Introduction: Monkeypox is an uncommon viral disease caused by a type of orthopoxvirus, and it is considered a zoonotic ailment, meaning it can be transmitted between humans and animals. Following the successful eradication of smallpox, the monkeypox virus has emerged as the most pathogenic virus within the orthopoxvirus family. Initially, it was primarily confined to central and west Africa. However, in 2022, the extensive outbreak of monkeypox in regions beyond its traditional boundaries raised significant concerns for the World Health Organization and the global health community.

Materials and Methods: This systematic review involved the utilization of Scopus, PubMed, Google Scholar, Web of Science, and Science Direct databases, spanning the time period from 1972 to February 18, 2023. The primary aim was to gather data regarding the correlation between prior vaccination against chickenpox and the subsequent development of immunity against monkeypox. Any articles that did not align with the specific objectives of this study were deliberately excluded during the research selection process.

Results: The majority of studies have established the efficacy of prior vaccination in providing protection against monkeypox. Given that monkeypox now represents a substantial threat to global health security, there is an imperative need for a prompt, multidisciplinary approach that involves veterinarians, physicians, virologists, and public health experts. This approach should facilitate swift follow-up actions, encompassing the development of vaccination methods, diagnostic assays, and other control strategies.

Conclusions: Given the demonstrated effectiveness of prior smallpox vaccination in safeguarding against monkeypox, it is imperative to prioritize the establishment of resources equipped with valuable knowledge for prevention initiatives. This includes the development of appropriate vaccines for proactive preparedness.

Keywords: Monkeypox, Smallpox Virus, Vaccination

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Introduction

Monkeypox (MPX) is a zoonotic disease that can be transmitted between humans and animals. The causative agent, the Monkeypox virus (MPXV), falls under the orthopoxvirus genus, and there exists a significant connection between MPX and the variola virus, which is responsible for causing smallpox infection.[1,2] It is believed that the origin of the infection can be attributed to an animal reservoir that remains unidentified. Alternatively, these occurrences may be a consequence of the growing encroachment of human populations into habitats inhabited by animal hosts.[3] Furthermore, a period of civil unrest and economic collapse compelled people to venture into the dense rainforest in search of food. Consequently, this increased the likelihood of contact with animals carrying the MPXV.[4] If vaccine protection diminishes within the population, it is expected that the average duration and the frequency of MPX epidemics will increase.[5]

Following the eradication of smallpox, the monkeypox virus has emerged as the most pathogenic virus within the poxvirus family, and it had been predominantly confined to central and West Africa. Due to challenges in surveillance in the rural areas of these regions, characterized by inadequate infrastructure, monitoring has been difficult. However, the extensive outbreak of MPX in various countries in 2022 has raised significant concerns for the World Health Organization.[6-9]

In 1970, the first human case of Human Monkeypox (HMPX) was identified in the Democratic Republic of Congo, an area where smallpox had been successfully eradicated approximately two years prior.[10] The initial human cases of MPX were documented beyond the African continent in 2003, occurring in the American Midwest. American patients were infected as a result of direct contact with domestic animals, particularly prairie dogs (Cynomys

species), which had come into contact with various rodents imported from Ghana.[11]

Since 1970, extensive epidemiological, virological, ecological, and public health research efforts have significantly improved the understanding of the MPXV and its associated human diseases. It is believed that transmission of the MPXV can occur through saliva or respiratory secretions, as well as through contact with lesions or skin secretions. Additionally, excretion of the virus in feces can serve as another potential source of exposure.[12] The clinical symptoms of MPX closely resemble those of smallpox, including primary symptoms such as high fever (smallpox often above 40 °C and MPX typically ranging between 40.5 °C and 38.5 °C), headache, general fatigue, skin rash, backache, stomach ache, sore throat, shortness of breath, cough, and in severe cases, convulsions. Other symptoms may include muscle and joint pain, loss of appetite, nausea, vomiting, lethargy, weakness, mood swings, and occasionally, confusion (though this is rare). It's important to note that not all individuals will manifest all of these symptoms, and the severity of symptoms may vary from person to person.

The primary distinguishing feature between monkeypox and smallpox is the presence of swollen lymph nodes (lymphadenopathy), which typically occurs early in the disease, often within 1 to 3 days after the onset of fever and usually coinciding with or preceding the appearance of the rash. Lesions develop concurrently with the rash and progress at a similar rate. While the distribution of lesions is primarily peripheral, in severe cases, they can cover the entire body.[13] The infection can persist for approximately four weeks until the lesions eventually scab over.

Additionally, patients may experience a broad spectrum of complications, such as secondary bacterial infections, respiratory distress, bronchopneumonia, gastrointestinal complications, dehydration, sepsis, encephalitis, and infection of the cornea, which could result in vision loss.[14] Clinical diagnosis and prevention of this disease pose significant challenges, particularly in underserved regions of Africa where MPX is prevalent. Transmission of the MPXV among close family contacts has been well-documented, with previous reports indicating up to six instances of transmission within families[15] Notably, the incidence of infection is considerably higher among individuals residing in households with MPXV patients, as well as among those without any documented history of prior vaccination.[16] Up to 11% of individuals who are infected and unvaccinated may succumb to the disease.[17] Nevertheless, the findings from a study indicated that the age of the patient and their prior smallpox vaccination status had minimal influence on the symptoms or the severity of the disease in individuals infected with MPXV during the 2003 outbreak in the United States.[18] As for vaccination, it's worth noting that while smallpox vaccination can offer protection against infection, this particular vaccination is not employed in regions where MPXV is endemic. This decision is primarily driven by cost-related factors and concerns regarding the use of vaccines that contain live viruses.[16]

This article aims to present data concerning cases of HMPX in individuals with a history of previous smallpox vaccination and explore the potential impact on the severity of complications in these cases. MPX outbreaks have been investigated in studies conducted towards the conclusion of smallpox eradication. However, with the discontinuation of routine smallpox vaccination and the gradual decline of herd immunity, new evaluations and preventative measures have become imperative.

Materials and Methods

The systematic review study gathered data regarding individuals infected with MPX who had a prior history of smallpox vaccination from articles published between 1972 and 2023. This review adheres to the PRISMA guidelines.[19] Figure 1 shows a summary of the stages of the study.

The search strategy was designed as follows: After identifying keywords aligning with the study's objectives, a systematic search was conducted across various electronic databases, including PubMed, Scopus, Web of Science (ISI), Google Scholar, and Science Direct. No language restrictions were applied.

For the PubMed database, the search strategy encompassed:

(Monkeypox [MeSH] OR monkeypox [tiab] OR "Monkeypox virus"[MeSH] OR “monkeypox” [tiab]) and (Vaccination [MeSH] OR Vaccination [tiab] OR “Active Immunization” [tiab] OR “Immunization, Active” [tiab]).

In the case of the Scopus database, the search strategy involved:

[TITLE-ABS-KEY (Monkeypox) OR TITLE-ABS-KEY (Monkeypox virus) OR TITLE-ABS-KEY ("monkeypox")] and [TITLE-ABS-KEY (Vaccination) OR TITLE-ABS-KEY ("Active Immunization") OR TITLE-ABS-KEY ("Immunization, Active")].

Furthermore, for the ISI database:

[TS = (Monkeypox) OR TS = ("Monkeypox virus") OR TS = ("monkeypox")] and [TS = (Vaccination) OR TS = ("Active Immunization") OR TS = ("Immunization, Active")].

Additionally, databases such as Science Direct and Google Scholar were also utilized to ensure comprehensive coverage and minimize the possibility of overlooking relevant articles.

Data Abstraction

The research search strategy was jointly conducted by each author, adhering to the requisite criteria for identifying pertinent studies. The procedure involved an individual examination of each article by each researcher, encompassing the initial assessment of article abstracts, the elimination of articles not aligned with the article's objectives, the categorization

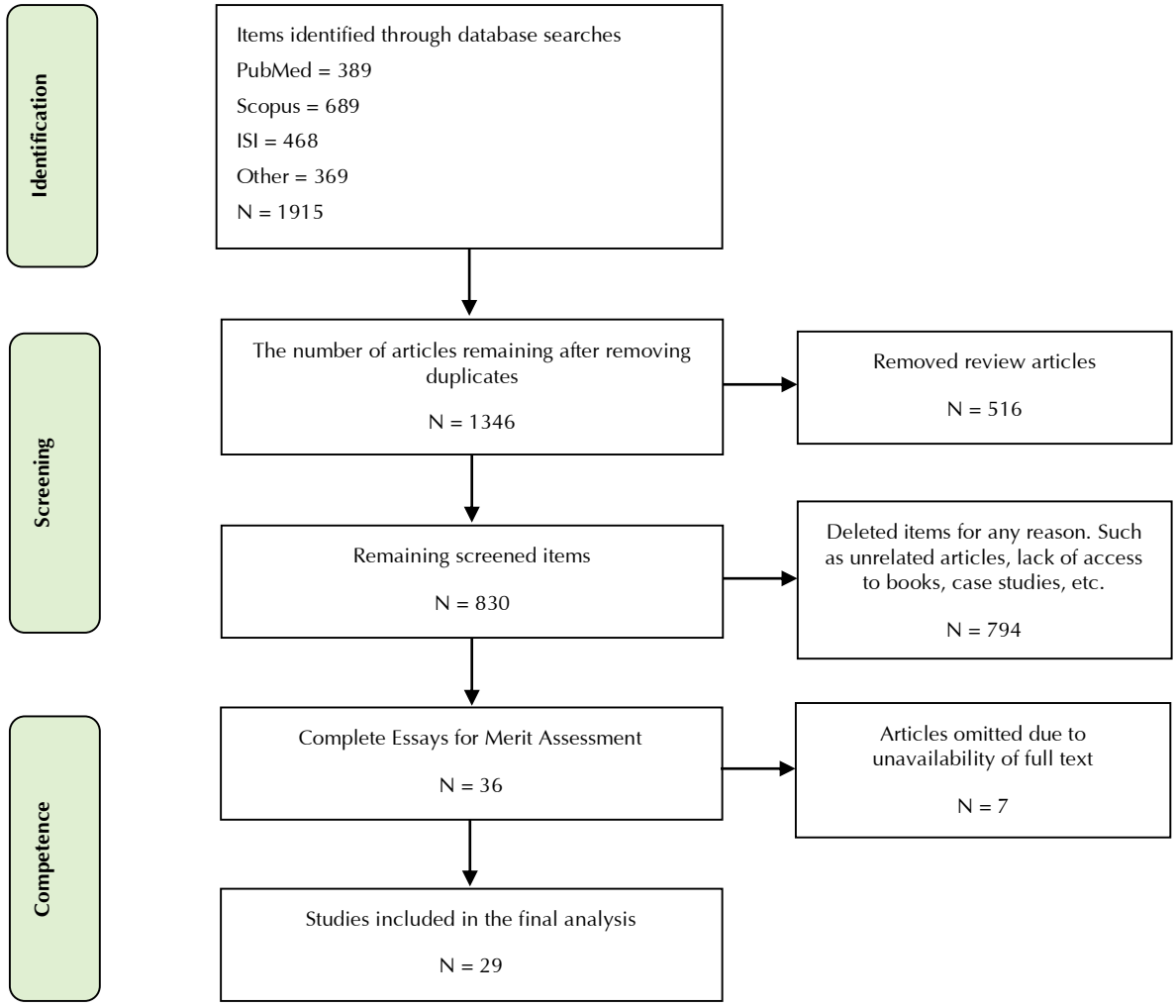

Figure1. Flowchart of the Steps of the Article Selection Method

of review articles, the retrieval of potentially overlooked articles, the extraction of items relevant to the article's subject matter from the final selection, and ultimately, the discussion and conclusion.

Inclusion Criteria

The articles included in this research were required to feature specific keywords. Moreover, they had to encompass at least one case of MPX in an individual who had received vaccination with MPXV prior to contracting the disease. Review articles were employed to augment the search for articles not covered by the initial databases.

Exclusion Criteria

Access to the full text of certain articles was unavailable, and extracting the desired data solely from the abstracts was not feasible. As a result, these articles had to be excluded from the study. Additionally, access to published books in this specific field was not possible, so they were omitted from consideration. Studies related to vaccination after infection with MPX (including individuals who were previously vaccinated and subsequently re-vaccinated against MPX were also excluded from the study. Furthermore, research related to incomplete vaccination and review articles were not included in the study.

Quality Assessment

The quality of each publication was evaluated independently by two authors, F.A and S.GH, using modified NIH and QualSyst quality assessment tools, with a maximum attainable score of 26.[20,21] The qualitative assessment of the findings from the articles incorporated into the study is presented in Table 1. Articles receiving scores of 25 and 26 were regarded as excellent, while those scoring between 20 and 24 were considered good. Scores of 18 and 19 were categorized as acceptable. Notably, all the articles in the study received scores exceeding 18, underscoring their favorable suitability for inclusion in this research.

Results

Study Selection

A total of 1915 eligible articles were initially obtained from

Table 1. Quality Assessment of Included Articles

Ref.	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Score	Overall Quality
[22]	Y	Y	P	Y	N	N	Y	Y	Y	Y	Y	Y	Y	21	Good
[23]	Y	Y	Y	Y	P	P	Y	Y	Y	Y	Y	Y	Y	24	Good
[24]	Y	Y	Y	Y	N	P	N	Y	Y	Y	Y	P	Y	20	Good
[25]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	24	Good
[1]	Y	Y	Y	Y	N	P	Y	Y	Y	Y	Y	Y	Y	23	Good
[17]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	24	Good
[2]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	26	Excellent
[26]	Y	Y	P	P	N	P	P	P	P	Y	Y	Y	Y	18	Acceptable
[4]	Y	P	N	Y	N	Y	N	Y	Y	Y	P	Y	Y	19	Acceptable
[27]	Y	Y	N	Y	P	N	Y	Y	Y	Y	Y	Y	Y	21	Good
[13]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	26	Excellent
[28]	Y	Y	Y	Y	Y	P	N	Y	Y	Y	Y	P	P	21	Good
[29]	Y	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	Y	Y	25	Excellent
[30]	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	22	Good
[31]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	26	Excellent
[32]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	26	Excellent
[33]	Y	Y	N	Y	P	Y	Y	Y	Y	Y	Y	Y	Y	23	Good
[15]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	24	Good
[34]	Y	Y	Y	Y	P	Y	N	Y	Y	N	Y	Y	Y	21	Good
[16]	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	P	Y	21	Good
[35]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	26	Excellent
[11]	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	Y	Y	Y	25	Excellent
[36]	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	Y	Y	Y	25	Excellent
[37]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	26	Excellent
[38]	Y	Y	Y	Y	N	P	P	Y	Y	Y	Y	Y	Y	22	Good
[39]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	26	Excellent
[40]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	26	Excellent
[41]	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	22	Good
[42]	Y	Y	Y	Y	N	P	Y	Y	Y	Y	Y	Y	Y	23	Good

Q: Question; Y: Yes (Score= 2); P: PARTIAL (Score=1); N: No (Score= 0)
Q1: Was the study question or objective clearly described?
Q2: Is the study design evident and appropriate?
Q3: Was the study population clearly and fully described (e.g., gender, age, and so on)?
Q4: Were the statistical methods or means of assessment well-described?
Q5: Are the inclusion and exclusion criteria for study participation specified?
Q6: Were the symptoms of the disease sufficiently described?
Q7: Was the primary source of the disease identified?
Q8: Was an adequate amount of time allocated for follow-up?
Q9: Was the method of data collection consistent for all participants?
Q10: Was transmission or non-transmission reported to family and other people?
Q11: Were the results well-described?
Q12: Are the criteria for drawing conclusions valid and reliable?
Q13: Do the conclusions align with the results?

the databases. Among these, 569 articles were excluded from consideration due to duplication. Consequently, from the remaining 1346 papers, 516 were identified as review articles. Furthermore, 794 articles were subsequently eliminated from the pool of candidates due to various reasons, including lack of relevance to the study's focus, inaccessibility owing to unavailability of required resources such as books, or their classification as case studies, among others. An additional 7 articles were discarded due to the unavailability of their full-text content.

In conclusion, the final analysis incorporated a total of 29 papers, which met the specified criteria for inclusion in the study (Figure 1).

Summary of Characteristics and Achievements of Studies

The summary of the characteristics of the studies from which data was extracted is provided in Table 2. This table includes information about the type of research, the number of individuals previously vaccinated against smallpox, gender, diagnostic method for MPXV, the average age of patients, the number of patients, the country where the study was conducted, and the year of the study.

Table 3, on the other hand, contains data related to the death rate in unvaccinated individuals against smallpox, the death rate in vaccinated individuals against smallpox, the transmission procedure, specific features, and reported disease symptoms.

In summary, the results are outlined as follows:

The first recorded case of MPX in humans was reported in August 1970. The affected individual was a 9-month-old child living in a village in the Democratic Republic of Congo. The family of the patient mentioned that they occasionally consumed monkeys as a culinary choice. However, they were unable to recall whether they had consumed monkey meat in the past month or whether the child had been in recent contact with a monkey. It was revealed through surveys that this child was the only one in the family who had not been vaccinated against smallpox.[43]

In the study conducted by Berryman et al. in 1978, there was evidence of secondary human-to-human transmission of MPX. Vaccination scar studies revealed relatively low levels of immunity in regions where cases of HMPX had been reported.

Among the 35 individuals afflicted by MPX, only four patients had a history of vaccination, and fortunately, all four of them survived the disease. On the other hand, among the 31 patients with no vaccination history, six individuals succumbed to the illness. Notably, in this study, nearly 60% of the children had not received the smallpox vaccination.

According to the findings of the article, the relatively low levels of immunity observed in areas where HMPX cases were reported are likely attributed to a decline in immunity levels or the absence of immunity against MPXV infection.[44]

During the years spanning from 1970 to 1975, Arita et al. reported 20 cases of HMPX in the tropical rainforests of West and Central Africa. Notably, two of these cases had received vaccination against smallpox. The clinical symptoms observed in the majority of the patients closely resembled those of smallpox. Out of the 20 patients, all but four, who had not received vaccination, survived the illness. Interestingly, even five years after being affected by the disease, serum samples collected from two of the infected individuals still contained antibodies specific to smallpox.[22]

Between 1970 and 1979, a total of 47 cases were reported in various countries, including Cameroon, Cote d'Ivoire, Liberia, Nigeria, Sierra Leone, and the Democratic Republic of the Congo. Notably, all of these cases occurred in the tropical rainforests of the Democratic Republic of the Congo. Among these 47 cases, 4 patients, which is approximately 9% of the total, had previously received vaccination against smallpox. Out of the 47 cases, 23 individuals experienced severe disease, and 8 of them, equivalent to 17%, sadly succumbed to the infection. It's worth mentioning that in some instances, the transmission of the disease took place within human-to-human clusters.[23]

In a study conducted from 1980 to 1984 in the Congo, involving 2510 contacts of 214 patients infected with MPX, it was observed that the majority of clinical MPX cases occurred in children under ten years of age. Interestingly, immunity appeared to have decreased even in individuals who had been vaccinated, and a significant number of these individuals were over 15 years old. Surprisingly, 16 cases of infection occurred among contacts who had been previously vaccinated. The overall attack rate for individuals without vaccination scars was 7.2%, which was notably different from the attack rate for those who had been previously vaccinated (0.9%). However, it's worth noting that many unvaccinated contacts, particularly those living in the same household under conditions of maximum exposure, not only avoided the disease but also remained uninfected. Statistical analysis of the vaccination history and close contacts revealed that the probability of contracting the disease among unvaccinated individuals at home was much higher (seven times higher) than among vaccinated contacts (four times higher) under normal conditions. Notably, the vast majority of unvaccinated household contacts were under the age of 14, and all secondary cases of MPX occurred in these children.[24]

The data relating to HMPX collected in the Congo from 1981 to 1986 to evaluate the rate of human transmission of MPXV showed that 2278 people who were in close contact with 245 MPX patients who were infected from an animal source and had close contact with each other, 93 people got sick. It was assumed that they were contaminated by known human sources. The rate of secondary attachment was related to the gender, age, habitat, and vaccination status of contacts. Following infection from a known human source, there was an overall 3% chance of becoming ill. The affected family was the main focal point for the transmission of the MPXV between humans. The highest attack rate (11.7%) among non-vaccinated family members (especially those who lived in the same house) occurred in the age group of 0-4 years and gradually decreased with increasing age. It seems that this relationship with age reflects close physical contact between very young siblings that decrease with age. However, most of the susceptible people who were close to patients in a confined space with poor ventilation did not get this disease.[5,25] In cases of primary infections, animal transmission was responsible for 72% of the cases, whereas human-to-human transmission accounted for the remaining 28% of cases.[25]

Another study conducted by Jezek et al. in 1983 examined the occurrence of five cases of HMPX in children from two families residing in the western region of Congo between May and July 1983. Out of these cases, four individuals had been infected by a previous human case, and the reported death rate was 14%. Notably, children under the age of ten accounted for 84% of these cases. The study found that smallpox vaccination provided protection from MPX, resulting in less severe rashes and superficial wounds in vaccinated individuals. The secondary attack rate among susceptible individuals in close proximity to the affected families was 10%, and among all susceptible contacts, it was 5%. This rate was significantly lower than that observed for smallpox, which typically ranged from 25% to 40%.[1]

In 1987, Jezek and colleagues conducted a study to investigate the clinical characteristics of 282 patients who had been infected with HMPX in the Congo between 1980 and 1985. The age range of the patients varied from one month to 69 years, with a striking observation that 90% of them were under 15 years old. The clinical presentation of the disease closely resembled both the typical and modified forms of smallpox. Notably, symptoms, signs, and morbidity differed significantly between patients who had been

vaccinated against smallpox and those who had not. Vaccinated patients exhibited significantly fewer skin lesions, and these lesions were smaller in size compared to non-vaccinated patients. Corneal opacity, which can lead to vision impairment, was reported in six unvaccinated children and one vaccinated child. Of these, one unvaccinated child suffered blindness in both eyes, while three unvaccinated children experienced blindness in one eye each. Additionally, two percent of unvaccinated patients displayed scars that altered the shape of their eyelids and lips. Lymphadenopathy, or enlargement of lymph nodes, was observed in 84% of non-vaccinated individuals and 53% of vaccinated individuals. Importantly, no deaths were reported among the vaccinated patients. In contrast, the crude mortality rate among unvaccinated patients was 11%, with the highest mortality rate (15%) observed in the youngest children.[17]

In another study conducted by Jezek and colleagues in 1986 in the Congo, it was observed that the majority of clinical and subclinical cases of MPX occurred in children under the age of 15. The statistical analysis from this study indicated that the history of vaccination and close contact influenced the probability of new MPX cases, and it revealed that non-vaccinated individuals were more likely to develop MPX compared to vaccinated individuals.[26]

In 1988, Jezek and colleagues reported epidemiological findings based on 91 MPX patients. The age range of these patients spanned from 7 months to 29 years, with a significant majority (93%) being under 15 years old. Among the patients, 11% had visible smallpox vaccination scars. Fortunately, deaths were sporadic, resulting in an overall death rate of 9%. In 70 cases, the source of infection was traced back to animals, while the remainder stemmed from human transmission. Notably, this disease occurred throughout the year. In the observed areas, the average annual incidence rate was 0.63 cases per 10,000 people, with notable variations in terms of age, time, and location. The average annual primary attack rate among unvaccinated individuals was 1.7 per 10,000, which was significantly different from the rate among vaccinated individuals (0.04 per 10,000). Moreover, the secondary attack rate for individuals without vaccination scars was 4.3%, which was significantly different from the rate among those who had been previously vaccinated (0.7%).[2]

A long-term outbreak of HMPX occurred in the Democratic Republic of Congo from 1996 to 1997. The first case was reported in mid-February 1996, but the full extent of the outbreak became apparent in late July when more individuals were infected. By August 30, 1996, a total of 71 suspected cases were reported in 13 villages. Among these, 11 cases were confirmed through laboratory testing, and tragically, six of these confirmed cases resulted in fatalities. Importantly, none of the individuals affected by the outbreak had been vaccinated against MPX prior to their infection.[3,45]

In a research study conducted by the World Health Organization, a total of 344 cases were identified from February 1996 to February 1997 in Congo. Subsequently, an additional 419 cases were identified during this period. Among the 419 newly identified cases, 22% had been in close contact with previous patients. Out of the initial 344 cases, 20 individuals (approximately 6%) showed evidence of vaccination scars, and 19 cases reported a history of previous chickenpox infection.[4]

In February 1997, a total of 88 active cases of HMPX were identified in the Congo region, spanning the previous 12 months. These cases were found in 12 villages. Orthopox virus-neutralizing antibodies were detected in the serum of 54% of the 72 patients examined and in 25% of 59 wild-caught animals, primarily squirrels. Additionally, 13 cases reported prior vaccination against smallpox. Tragically, all three cases that resulted in death were children under the age of three years old. It appears that, in 1983, following the global eradication of smallpox, the proportion of individuals susceptible to HMPX had increased.[27] In another study involving 34 patients with MPX, it's noteworthy that none of these patients succumbed to the illness. Interestingly, the study found that previous smallpox vaccination did not appear to be linked to the severity of the disease or the need for hospitalization. However, it's worth mentioning that a higher number of children were admitted to intensive care units (ICU) compared to adults. This observation may suggest a more severe form of the disease among children or differences in the standard of care provided to pediatric and adult patients.[13]

In 2003, a total of 12 cases of HMPX were observed, comprising 3 confirmed cases, eight possible cases, and 1 suspected case. It's notable that all of these cases were individuals under the age of 18, except for the suspected case.[7,28] During this outbreak, there was clear evidence of human-to-human transmission, with at least seven generations of virus transmission occurring, marking the longest chain of transmission ever recorded in such an outbreak. The disease manifestations were relatively severe, resulting in one fatality during this outbreak. Interestingly, it was found that vaccination against smallpox, administered 3 to 19 years prior to exposure, offered up to 85% protection against MPX.[28]

In June 2003, an outbreak of MPX in the Midwestern United States marked the first documented human infection in the western hemisphere. Within a family with three reported patients, one case had a history of previous smallpox vaccination and exhibited milder symptoms compared to the other affected individuals. This observation suggests that the severity of the reported disease may be influenced by the timing and age of previous smallpox vaccination.[29]

Following the 2003 outbreak of MPX in the United States, the role of prior immunity due to smallpox vaccination and

acquired immunity in susceptibility to HMPX was evaluated by Karim et al. in 2007. The study measured clinical results related to IgG, IgM, CD4, and Orthopoxvirus-specific B lymphocytes at 7-14 weeks and one year after exposure. The findings indicated that vaccination against smallpox did not offer complete protection against MPX. In previously vaccinated individuals who had contact with MPX cases, there were low levels of anti-orthopoxvirus IgG, CD4, and B-cell responses, with many lacking IgM or CD8 responses. Prior immunity, assessed through high levels of anti-orthopoxvirus IgG and childhood smallpox vaccination, was associated with milder disease. For previous MPX cases, IgM, anti-orthopoxvirus antibodies, and changes in anti-orthopoxvirus IgG, CD4, CD8, or B-cell responses served as markers of recent infection. In MPX cases, both vaccinated and unvaccinated, anti-orthopoxvirus IgG and CD8 responses, along with IgG, CD4, and memory B-cell responses, indicated vaccine-induced immunity.[30]

In the 2007 report by Reynolds and colleagues on the prevalence of MPX in America in 2003, regardless of age or the characteristics of exposure, it was found that a history of smallpox vaccination, particularly if it had occurred more than 25 years ago, provided protection against MPX infection. Individuals vaccinated against smallpox who contracted MPX tended to experience a relatively mild form of the disease. These individuals typically did not require hospitalization and had fewer than 25 lesions. On the other hand, unvaccinated individuals were more likely to have a higher frequency of skin abrasions and breaks. It was also noted that contact with a sick animal significantly increased the risk of developing MPX, regardless of an individual's smallpox vaccination status.[31]

In May and June 2003, an outbreak of febrile illness with vesicopustular eruptions was observed in individuals in the United States who had been in contact with sick prairie dogs. Notably, among the 11 patients affected, 6 were born after 1972, and thankfully, none of them lost their lives.[32] It's important to highlight that this outcome contrasts with the 4-22% mortality rate reported during the outbreak of the disease in Africa. This difference in mortality rates may be related to the cessation of routine smallpox vaccination among civilians.[27,46]

In the study conducted by Hammarlund and colleagues in 2005, 20 individuals were reported to have been infected with MPX. Out of these, eight individuals had a history of smallpox vaccination, and three of them had been vaccinated against smallpox 13, 29, and 48 years before contracting MPX. Remarkably, these three individuals did not exhibit any detectable disease symptoms, suggesting that their smallpox vaccination had conferred immunity against MPXV that could potentially be maintained for several decades.

Additionally, the study found that antiviral antibody and T-cell responses could persist for up to 75 years after smallpox vaccination, further highlighting the long-lasting effects of smallpox vaccination on immunity.[33]

Between September 20, 2005, and January 31, 2006, a total of 49 cases were reported in Sudan, comprising 10 confirmed cases, nine probable cases, and 30 suspected cases. Among these 30 suspected patients, 18 cases could not be examined. However, after a reevaluation, 12 cases were reclassified as non-patients. Among these 12 individuals, two, aged 50 and 40, tested positive for IgG, which was attributed to previous smallpox vaccination. Additionally, six patients (0.75%) reported oral lesions, which was in line with the frequency of reported oral lesions observed in unvaccinated patients in the Democratic Republic of the Congo during the years 1981-1986.[15]

From 2006 to 2007, an active surveillance program in Congo identified a total of 633 cases of MPX. Interestingly, 152 of these cases (13%) were concurrent cases of MPX and varicella-zoster (VZ) virus among 1158 suspected cases of HMPX. Out of these cases, 30 individuals had a history of previous smallpox vaccination. Epidemiologically, the occurrence of the disease appeared to be associated with individuals who had not been vaccinated against smallpox. Notably, a significant number of MPX patients were children under the age of 14 who had not had the opportunity to receive smallpox vaccination.[34]

In the second half of 2013, the Congo witnessed a substantial 600-fold increase in MPX cases. Among a total of 154 cases, 104 were deemed possible and 50 were confirmed cases, accounting for 48.1% of the total. Disturbingly, nine families experienced more than one transmission event, indicating a high rate of attack and transmission of the virus. It's important to note that vaccination efforts were primarily targeted at individuals over 33 years old. Among 16 investigated families, 15% of infected family members had evidence of previous smallpox vaccination. Notably, the vaccination status and age over 33 were closely correlated. Although smallpox vaccination has the potential to offer protection against MPX infection, it was not routinely employed in MPXV-endemic areas. The decision not to use this vaccine was often influenced by cost considerations and concerns regarding the use of a live vaccine virus, as well as potential issues related to immunity.[16]

In a study conducted in Congo, 26 patients who were either confirmed or suspected cases were identified. Among these cases, 19.2% (approximately 5 out of 26) had smallpox vaccination scars. Notably, the overall attack rate for MPX was lower among vaccinated individuals, standing at 0.95 cases per 1000 people, compared to non-vaccinated individuals, who had an attack rate of 3.6 cases per 1000 people.[11]

Whitehouse et al. reported a total of 1057 confirmed cases based on Congolese surveillance data from 2015 to 2011.

Table2. Significant Details of the Studies Were Incorporated in the Present Review

No	Year of the study	Country	The number of patient	Average age of patients	Diagnostic method for MPXV	Gender	The number of people previously vaccinated against smallpox	Type of research	Ref.
1	1970-1979	Congo Liberia Nigeria Cote dlivoire Cameron Sierra leone	In one report 35 cases, in another report 47 cases	From 7 months to 40 years	Measurement of specific antibody of MPX and isolation of MPXV DNA	Female = 23 Male = 24 Out of 5 cases. 4 cases were adults and female	For people, including 35,30,24 and 8 years old, they were vaccinated 3 years before contracting the disease	Report	[23]
2	1970-1975	Congo Liberia Nigeria Cote dlivoire Sierra leone	20	13 children under 5 years old, 2 cases between 6-15, 5 cases of adults	Isolation of MPXV SEM, Specific antibody of MPXV	Female = 11 Male = 9	2 cases including 24 &30 years old	Report	[22]
3	1981-1986	Congo	22+24 primary cases and 62 secondary cases	Out 0f 214 patients: 0-4 (111) (87) 5-14 and 16 cases were over 15 years' old	Specific antibody of MPXV and serology	ND	Out of 214; 28 person were vaccinated, (1869 contacts were vaccinated)	Original Research	[24]
4	1981-1986	Congo	338	3 months to 69 years' old (86% <10 years old)	Virus observation with electron microscopy, ELISA test, fluorescent antibody, hemagglutination test	Female = 156 Male = 182	43 people (13%)	Report	[25]
5	1983	Congo	5	Patients from 18 months to 7 years old	Radioimmunoassay tests for absorption and isolation of MPVX from skin lesion	Female = 1 Male = 4	2 people	Original Research	[1]
6	1980-1985	Congo	282	Patients from 1 month to 69 years old (90% <15 years)	Electron microscopy, ELISA test, fluorescent antibody, tissue culture and serology, culture on alantoic membrane of chicken	Female = 139 Male = 143 (the most under 4 years old)	32 people (11.3%)	Original Research	[17]
7	1981-1985	Congo	91	Patients from 7 months to 29 years' old (93% <15 years)	NA	NA	10 people (11%)	Original Research	[2]
8	1996-1997	Congo	92	25 patients (27.2%) were 15 years old or older	Isolation of virus and antibody studies	Female = 41 Male = 51	15 (17.9%) patients of which 13 people were 25 (86.6%) years old or older	Original Research	[26]
9	1996-1997	Congo	419	85% of the cases were under 16 years old	Isolation of virus from the wound	Male = 55%	20 people(6%) had previous vaccinations and 19 cases had history of chickenpox	Review Article	[4]
10	1997	Congo	88	5-62 years old.	Isolation of virus,	Female = 33	13 cases(over 20 years old)	Original	[27]

				average 10 years and with a higher rate in children less than 15 years old	hemagglutination test and IgG investigation	Male = 50		Research	
11	2003	Congo	32	6 to 47 years old (average 26 years) 71% of people over 18 years old	Viral culture, PCR MPXV ،electron microscopy, immunohistochemical analysis	Female = 16 Male = 18	7 patients from 33 to 47 years old	Original Research	[13]
12	2003	Congo	12	Except one person, the others were under 18 years old	Molecular analysis, virology ,serology test	Female = 4 Male = 8	3 people	Original Research	[28]
13	2003	America	3	6.30 and 33 years old	DNA PCR, viral culture, serology test, histopathology, immunohistovhemical	Female = 2 (mother and girl) Male = 1 (father)	1 person (family's father)	Original Research	[29]
14	2003	America	72	Patients from 12 to 60 years old	Measures the level of IgG and IgM, ELISA	ND	12 cases had history of vaccination	Original Research	[30]
15	2003	America	30 possible confirmed cases	6-45 years old. 10 cases were under 18 years old and 20 cases were over 18 years old (Average age 25 years)	Isolation of MPXV, Nucleic acid detection of MPXV, electron microscopy, immunoglobulin analysis (e.g. IgM and IgG)	Female = 17 Male = 13	6 cases	Original Research	[31]
16	2003	America	11	3-43 years	Immunohistochemical, PCR, DNA virus extraction, electron microscopy	Female = 6 Male = 5	5 cases	Original Research	[32]
17	2005	America	20	ND	Immunohistochemical, PCR, virus culture, ELISA electron microscopy	ND	8 People, of which 3 had no symptoms	Review Article	[33]
18	2005-2006	Sudan	49 cases (10 confirmed cases , 9 possible, 30 suspected, and 19 finall)	8-50 years old	ELISA and virus isolation ،PCR	Female = 10 Male = 9	The unconfirmed suspected persons, 2 cases were IgG positive, which was attributed to the immunity of previous vaccination	Original Research	[15]
19	2006-2007	Congo	633 cases+ 152 simultaneous cases with MPXV and varicella zoster virus	Patients under 5 to 80 years old	qPCR after the extraction of viral DNA	Only had MPX (Female 245, male 388), MPX and varicella zoster (female 60,male 92)	19 people only had MPX and 11people had MPX and VZ	Original Research	[34]
20	2013	Congo	50 cases	Patients from 4 months to 68 years old (average 10 years old)	PCR and detection of virus DNA	ND	9 people	Original Research	[16]

				17.7%<5 years old					
21	2011-2015	Congo	1057 cases, 775 cases had MPVX and 169 simultaneous cases with MPXV and VZ, 113 samples were not available	Patients from 1 month to 79 years old(the average 14 years old)	PCR and detection of virus DNA	Female = 568 Male = 486	97 cases(64 man and 33 woman)	Original Research	[35]
22	2016	Congo	26 cases	Patients from 1 to 58 years old (the most effect on 10 and 21-30 years old groups)	PCR and detection of virus DNA	Man = 53.8%	5 people	Original Research	[11]
23	2018	England	6 cases	ND	PCR and detection of virus DNA	All of them were men	1 case	Original Research	[36]
24	2022	Italy, Australia, Czech Republic, Portugal, Britain	124 cases. There was just 32 cases available,(4 cases from Italy, 27 cases from Portugal, 1 case from Australia)	Most people were in their 30s: 43.75% of 30-year-olds, 9.38% and 3.13% of people were in their forties and fifties, and 21.88% were in their twenties, respectively. In (9.38%), it was unclear.	PCR and orthopox virus specific antibodies	All of them were men. There is a high probability of sexual transmission	People (one from Italy another from Portugal	a preliminary pooled data analysis and literature review	[37]
25	2022	Italy	4 cases	All of them 30 years old	MPXV DNA by PCR	Male	One case	Original Research	[38]
26	2022	Portugal	27 cases	Patient from 20 -59 years old(3 cases were unknown)	MPXV DNA by PCR	Male	One middle aged case	Original Research	[39]
27	2022	Spain	185	Average 38·7	MPXV DNA by PCR	Male	20 cases (probably)	Original Research	[40]
28	2022	United States	1195	Median age was 35 years	ND	Male = 1181 Female = 10 Unknown = 4	48 cases	Original Research	[41]
29	2022	Austria	ND	41- ≥100	ND	ND	ND	Original Research	[42]

Table3. Clinical Features of Individuals with Monkeypox

No	Reported disease symptoms	Specific features	Transmission procedure	Death rate in vaccinated people against smallpox	Death rate in unvaccinated people against smallpox	Ref.
1	High fever rash	-	Probably secondary human to human transmission have occurred	zero	8 children between 7 months to 7years old (17%)	[23]
2	Rash (the other symptoms were not defined)	-	The primary source of monkeys may have been human to human transmission(6 cases were family, 1 case was close to sick person)	zero	4	[22]
3	Fever, rash, lymphadenopathy, conjunctivae	Difficulty breathing	The secondary transmission is human to human and the primary source is from animals	Zero (it not exactly determined)	1 case+6 cases (it was not determined whether vaccinated or not)	[24]
4	Fever, rash, lymphadenopathy, mouth ulcer, coughing, vomiting and diarrhea	Bronchopneumonia, ARDS, keratitis, encephalitis, septicemia	Primary infections from animals were responsible for 72% of transmission, while human to human transmission comprised 28%	zero	33 people (unvaccinated children from 3 months to 8 years old). There was no difference between the human and animal resources	[25]
5	Fever, rash, lymphadenopathy, edema	-	Each of the 4 other cases had infected by previous human case	zero	1 death	[1]
6	Fever, rash, lymphadenopathy, severe headache, back pain, general weakness, diarrhea, vomiting, dehydration	Bronchopneumonia, blindness, keratitis, encephalitis, cornea ulcer	ND	zero	27 cases. All children between 3 months and 8 years old	[17]
7	NA	NA	The source of contamination was suspected in 70 animal cases and in the remaining 21 human cases	NA	The overall death rate was 9% , vaccination status was unknown	[2]
8	Rash	-	Out of 89 patients, information was available for them, 75 people reported contact with another patients 7-21 days before illness.	zero	3 cases were under 3 years old	[26]
9	98% Fever, rash, 69% lymphadenopathy, 50% mouth ulcer 41% coughing, 63% sore throat and 11% diarrhea	Alopecia, darkling of the cornea	2cases without contact, one case with contact, 22% of next 419 cases identified were infected due to contact	؟	5cases; 4-8 years old (the death rate 1.5%). Within 3 weeks of the onset of rashes. Their vaccination status was unknown.	[4]
10	Fever, rash, lymphadenopathy,	Alopecia	Human to human transmission and animal to human transmission	zero	3 cases, all of them happened in children under 3 years old	[27]
11	Fever, rash, sweating, chills, lymphadenopathy, headache, stiff neck, red eyes, runny nose, sore throat, cough, wheezing, shortness of breath, chest pain, nausea and/or vomiting, abdominal and back pain, joint pain Confusion and conjunctivitis	Myalgia, encephalopathy, and retropharyngeal abscess	No human –human- transmission reported.	zero	zero	[13]
12	Fever, rash, lethargy, irritability, back pain, lymphadenopathy, headache, cold, cough	Kidney infection, coryza	Person to person transmission was evident and the disease manifestation were relatively severe	zero	1 death case	[28]
13	Fever, rash, sore throat, headache, anorexia	Encephalopathy and severe nerve infection, convulsions, muscle stiffness	Transmission form dog to human	zero	zero	[29]
14	Fever, rash, lymphadenopathy, headache,	-	Transmission through direct contact with	zero	zero	[30]

	cough, sore throat, sweating		dog or transmission human to human.			
15	Fever, conjunctivitis, respiratory symptoms and skin rash, chills and/or sweating, headache, back pain, lymphadenopathy, mouth sores, sore throat, cough, and shortness of breath	-	The possibility of human-to-human transmission	zero	zero	[31]
16	Fever, rash, headache, sweating, chills, nausea, diarrhea, persistent cough, lymphadenopathy, sore throat, nasal congestion, weakness, mild chest congestion, back pain	Pharyngitis, hypertrophy of tonsils, myalgia. Blepharitis	The virus was transmitted through contact with dogs. However,2 patients cared for their infected child (possible person-to-person transmission)	zero	zero	[32]
17	Fever, rash, headache, back pain, lymphadenopathy, sore throat, cold, shortness of breath	-	It has been transmitted to humans through indirect contact, possibly as fomites or aerosol exposure.	zero	zero	[33]
18	Fever, rash, cough, cold headache, nausea, diarrhea, loss of appetite, red eyes, abdominal pain, mouth sores, severe fatigue, lymphadenopathy, inflammation of nasal mucous membranes, throat and joint pain.	Difficulty breathing, difficulty swallowing. Itching and cervical and/or inguinal adenopathy	Human-to-human transmission up to 5 generations	zero	zero	[15]
19	Fever, rash, diarrhea, and vomiting, persistent cough, lymphadenopathy, mouth ulcers, abdominal pain, joint pain, mild chest tightness, back pain,,	Convulsions, keloid, alopecia, blurred vision	ND	zero	zero	[34]
20	High fever, rash, lymphadenopathy	-	9 families showed more than 1 transmission event (high rate of attack and transmission).	zero	10	[16]
21	fever, rash, lymphadenopathy		Contact with animals and human-to-human transmission	zero	zero	[35]
22	fever, rash, adenopathy, cold, itching, headache	Dysphagia, myalgia	The first patient had consumed the meat of a dead squirrel. 23 patients (88.5%) were secondary cases.	zero (it was not clear whether the first patient was vaccinated or not)	The first patient (36 years old) and a 12-month-old baby died.	[11]
23	fever, rash, lymphadenopathy	-	Transferred to 4 people All four patients had sex with other men. Two of them had HIV infection.	zero	zero	[36]
24	Fever, rash, lymphadenopathy, fatigue, back pain, headache and diarrhea	myalgia	Contact with animals and human-to-human transmission	zero	zero	[37]
25	Fever, rash, lymphadenopathy, diarrhea, fatigue, and headache	myalgia	All cases were infected through sexual intercourse with humans.	zero	zero	[38]
26	Fever, asthenia and fatigue, headache, anogenital ulcers and vesicles, exanthema, lymphadenopathy	Exanthema, myalgia	Human to human (sexually transmitted infections)	zero	zero	[39]
27	All patients had systemic symptoms (100%) like: lymphadenopathy (56%), fever (54%), asthenia (44%), and headache (32%).	Lesions, monkeypox whitlows, myalgia	Human to human (sexually transmitted infections)	zero	zero	[40]
28	Rash (100%), fever (63%), chills (59%), and lymphadenopathy (59%), Vomiting or nausea	Rectal pain, Pus or blood in stools, Tenesmus,myalgia	Human to human (often sexually transmitted infections)	zero	zero	[41]
29	ND	ND	transmitted from Human to human (Often sexually)	ND	ND	[42]

The data revealed the highest incidence of MPX in males aged 10 to 19 years, a demographic that had more frequent contact with animals. Interestingly, the incidence of this disease was lower among individuals who had received the smallpox vaccine compared to those who were not vaccinated. However, there were no notable differences observed in terms of age groups, the number of skin lesions, or the severity of the lesions between the vaccinated and non-vaccinated groups.[35]

In September 2018, a case of MPX transmission occurred from a patient to a healthcare worker in the United Kingdom, likely due to contact with contaminated bedding. In response, critical infection control measures, including vaccination, daily care, and home isolation, were swiftly implemented for 134 patients. Out of these individuals, four patients fell ill, but fortunately, all of them survived. One of these patients had been vaccinated prior to the onset of symptoms, while the remaining patients received vaccination after the onset of symptoms, with more than four days passing since their last contact with one of the infected patients. Unfortunately, in this particular case, the desired results were not achieved, and it's possible that the vaccination occurred too late to effectively prevent MPX in these individuals.[36]

In Mathieu's report, data was gathered from six clusters located in Italy, Australia, the Czech Republic, Portugal, and the United Kingdom. These clusters collectively accounted for a total of 124 MPX cases, with detailed information available for 35 of these cases. This ongoing epidemic differed from previous outbreaks in several key aspects, including the age of those affected, with 54.29% of cases occurring in individuals in their 30s. Additionally, there were notable differences in terms of gender, as the majority of cases were males. The risk factors contributing to the transmission of the virus also differed, and the potential for sexual transmission was significantly high. Remarkably, only two of the individuals affected had a history of previous vaccination against the disease, further underscoring the distinctive characteristics of this particular outbreak.[37] In the report by Antinori et al. in 2022, it was noted that among the four infected individuals in Italy, two of them had a history of previous vaccination. Importantly, all of these cases had been infected through sexual intercourse with other humans.[38] The two studies presented above indicated that the affected subjects were primarily young individuals. This is because older people were generally protected against MPX due to their prior smallpox vaccination.[37,38] Furthermore, among the 27 reported cases of infection in Portugal, only one case had a history of previous vaccination. These MPX outbreaks in Portugal highlight the ongoing transmission within a susceptible population that has not had the benefit of prior exposure to smallpox vaccination.[39]

In the report by Català et al. in 2022, it was noted that all 185 patients with MPX exhibited systemic symptoms. Among these patients, 10% were born before 1972 and were therefore highly likely to have received smallpox vaccination. Interestingly, there were no significant differences found in the extent or number of skin lesions between patients who had received smallpox vaccination and those who had not. Importantly, none of the patients succumbed to the disease. The report suggested that the most likely mechanism of transmission for MPX in this context was through contact during sexual activity.[40]

In another research study involving 339 individuals, 48 of them (14%) reported having received the smallpox vaccine at some point in the past. Notably, there were no reported deaths among these individuals.However, it's important to note that this particular report did not determine the effects of previous vaccination on the severity of the disease.[41]

Spott et al. (2022) employed a modified model to evaluate the impact of smallpox vaccine-induced protection, age-dependent vaccine-induced immunity against HMPX, and the likelihood of infection based on age within the general population of Vienna, Austria. Their findings revealed that among individuals born before 1981, the average protective effect stemming from the vaccine was estimated to be 50.4%. However, among individuals born after 1981, there was no observed protection conferred by the vaccine.[42]

The key details of the current review studies and the associated clinical features have been summarized in Tables 2 and 3.

Discussion

As per the findings of the current research, previous vaccination against smallpox can significantly contribute to symptom reduction and a substantial decrease in mortality. In reports where the number of deaths was accurately attributed to either the vaccinated or non-vaccinated groups, individuals with previous vaccination had zero reported deaths.[1-13,15-17,22,23,25-39,44] The observed shift in transmission dynamics may be attributed to the rise in the number of susceptible individuals resulting from the discontinuation of the smallpox vaccination program. While previous vaccination can provide protection to populations at the highest risk of infection, it's important to note that, due to severe side effects associated with vaccination, special attention should be given, particularly in cases involving individuals with HIV immunodeficiency.[26]

This study was conducted after the eradication of smallpox and demonstrated that prior smallpox vaccination can offer protection against MPXV infection.[5] Nonetheless, smallpox vaccines have not been administered due to concerns regarding their potential side effects.[47] For instance, the presence of human immunodeficiency virus (HIV) infection, unforeseen outbreaks, or other forms of immunosuppression in MPX endemic regions in Africa raises concerns about the

potential for severe vaccine-related complications, such as Eczema vaccinatum, a condition where uncontrolled replication of the vaccinia virus can lead to fatalities. When the occurrence of MPX extended beyond the African continent and reached the United States in 2003, it challenged the previous assumption that the disease was confined to specific geographic regions. The summary of the results discussed above indicates a growing number of MPX cases in recent years, which have been linked to widespread geographic events. While many of these cases occur individually or in small clusters, there have also been instances of large outbreaks involving numerous individuals across extensive geographic areas.[16]

While the study found that a history of smallpox vaccination was linked to a lower risk of infection, interpreting this finding accurately can be challenging without accounting for factors like age or previous exposure history. Human epidemiological studies have demonstrated that both age and smallpox vaccination status play a significant role in influencing susceptibility to MPX. In the results we have reported, it's evident that the age of infection in Africa was primarily associated with unvaccinated children aged 5 to 15 years.[1,17,24,27] Furthermore, both human and animal studies indicate that the sensitivity and severity of MPX disease are more pronounced in younger individuals.[29] In contrast to the African epidemics, the majority of cases reported in the United States were among adults. These distinctive characteristics help explain some of the observed differences in clinical descriptions between patients in the United States and those in Africa. Unlike the MPX outbreak in Africa, where a disproportionate number of children were affected, none of whom had immunity from the smallpox vaccine, the cases in the USA predominantly occurred in adults. Furthermore, nearly a third of these adults had received the smallpox vaccine before 1972.[13] Additionally, in one report, a significant portion of the infected individuals were around 30 years old. This age group was affected because all of these individuals had contracted the infection through sexual contact.[37] Another noteworthy aspect related to the risk of MPXV infection is the high durability of protection, which can last for more than 75 years.[33] In one report, it was indicated that smallpox vaccination administered between 3 to 19 years before a person's exposure to the smallpox virus can be up to 85% effective in providing protection against infection with the MPXV.[3] According to the report by Paluku et al. in 1987, out of 282 patients who were infected with this disease from 1980 to 1985, 32 of them had visible vaccination scars. The existing immunity in these individuals notably reduced the severity and frequency of symptoms and complications. However, it was observed that immunity appeared to be diminishing in vaccinated individuals over time.[17]

Human-to-human transmission may occur through close contact with the skin lesions of an infected person or exposure to respiratory droplets during face-to-face contact.[36] We observed that with this mode of transmission, it often affects multiple members within a family.[3,11,15,16,22,23,26,27,32] The higher attack rate among female family members is likely a result of the close contact they have with patients, as they often take on caregiving roles. This discrepancy is probably not due to gender differences in susceptibility to the MPXV. Men are more likely to be affected, possibly because unvaccinated young boys are involved in activities like trapping small rodents and playing with the carcasses of monkeys and other animals brought home by hunters. Additionally, in larger families, there is a likelihood for the children within the same family to have close relationships with each other.[25] It's important to note that an increased prevalence of MPX in humans, especially among immune-compromised individuals, could potentially create more opportunities for the MPX virus to acquire mutations that might enhance its ability to infect human hosts. This, in turn, could potentially lead to increased transmission and pathogenicity of the virus.[47] In the end, a combination of vaccination and a vigilant surveillance program resulted in the global eradication of smallpox. Regrettably, due to the existence of animal reservoirs, eradicating MPX is not feasible. Nonetheless, it has been observed that prior vaccination with the smallpox vaccine offers robust protection against MPX virus infection.[5,22,24]

Conversely, the similarities of MPXV to other viruses within the smallpox family, coupled with the diminishing immunity in populations post-smallpox vaccination, have raised concerns about the potential use of this virus as a biological weapon. As a result, MPXV has been classified under the highest threat category by national health institutes, alongside other smallpox viruses. While MPX outbreaks are typically not the result of bioterrorism, the occurrence of an MPX disease outbreak in a new, previously disease-free region of the world, as seen in the 2003 MPX outbreak in the United States, can elicit fear and apprehension.[48] Therefore, it is advisable to maintain ongoing surveillance and implement local disease control measures to monitor and minimize the risk of both primary and secondary infection spread. These measures can include practices like restricting care and avoiding contact with dead or ill wild animals. Furthermore, additional risk reduction strategies are necessary, guided by the results of continuous surveillance, vaccination efforts, and other control strategies.[15] Currently, there are two vaccines available for preventing orthopox virus infection, namely ACAM2000 and JYNNEOS. JYNNEOS, which is an attenuated virus with low replication and fewer side effects, is the preferred choice. This vaccine regimen consists of two doses administered 28 days apart. It's important to note that immunity doesn't develop until two weeks after the second dose.[49,50]

Highly attenuated strains, such as the Ankara-modified vaccinia virus (MVA), are currently under assessment in both human and animal models. Previous research has demonstrated that priming and boosting with MVA provide protection for more than two years in an MPXV challenge model, which is an encouraging and promising finding.[51]

Conclusion

In conclusion, based on the findings of the present research regarding the effectiveness of prior MPX vaccination in enhancing immunity, reducing the severity of symptoms, lowering the attack rate, and decreasing mortality, it can be inferred that vaccination is likely to be a crucial strategy for mitigating the risks associated with HMPX. Vaccination strategies encompass pre-exposure vaccination, post-exposure prophylaxis, and vaccination of close contacts.

Authors' Contributions

FA, SGh, and MAJ collaborated in collecting and categorizing the pertinent articles and contributed to drafting the main text. SGh and FA initiated the concept for the article, with SGh overseeing the team.

Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

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