microorganisms

MDPI

Review

Human Monkeypox: A Comprehensive and Public Health implications

Francesco Di Gennaro*[1], Nicola Veronese[2], Claudia Marotta[3], Jae Il Shin[4], Ai Koyanagi[5], Andrea Silenzi[2], Mario Antunes[6], Annalisa Saracino[1], Davide Fiore Bavaro[1], Pinar Soysal[7], Francesco Vladimiro Segala[1], Laurie Butler[8], Mario Barbagallo[2], Yvonne Barnett[8], Christopher Parris[8], Emanuele Nicastri[9], Damiano Pizzol[10] and Lee Smith[11]

1Clinic of Infectious Diseases, University of Bari, University Hospital Policlinico, Bari, Italy. F.D.G (Francesco.digennaro1@uniba.it); A.S. (annalisa.saracino@uniba.it); D.F.B (davidebavaro@gmail.com) FVS (fvsegala@gmail.com)

2 Geriatric Unit, Department of Internal Medicine and Geriatrics, University of Palermo, Palermo, Italy N.V.(ilmannato@gmail.com); M.B. (mario.barbagallo@unipa.it)

3 General Directorate of Health Prevention, Ministry of Health, 00144 Rome, Italy. C.M (c.marotta@sanita.it); A.S. (a.silenzi@sanita.it)

4 Department of Pediatrics, Yonsei University College of Medicine, Seoul 03722, Korea. J.I. S. (shin pedshin2000@gmail.com)

5 Research and Development Unit, Parc Sanitari Sant Joan de Déu, CIBERSAM, ISCIII, Barcelona, Spain; ICREA, Pg. Lluis Companys 23, 08010, Barcelona, Spain. A.K. (ai.koyanagi@sjd.es)

6 Catholic University of Mozambique, Beira, Mozambique M.A. (majomantu@gmail.com)

7 Department of Geriatric Medicine, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Turkey; P.S. (dr.pinarysoysal@hotmail.com)

8 Faculty of Science and Engineering, Anglia Ruskin University, Cambridge, UK; L.B. (laurie.butler@aru.ac.uk); Y.B. (yvonne.barnett@aru.ac.uk); C.P. (chris.parris@aru.ac.uk)

9. National Institute for Infectious Diseases, Lazzaro Spallanzani, IRCCS, Via Portuense, 292, Rome 00149, Italy. E.N. (e.nicastri@inmi.it)

10 Italian Agency for Development Cooperation – Khartoum, Sudan D.P. (damianopizzol8@gmail.com)

11 Centre for Health Performance and Wellbeing, Anglia Ruskin University, Cambridge, UK, CB1 1PT L.S. (lee.smith@aru.ac.uk)

* Correspondence: francesco.digennaro1@uniba.it

Abstract: Recently, many cases of monkeypox were reported from several non-endemic countries in Europe, North America and Oceania, representing an unusual and alarming public health issue, particularly considering that it is not directly related to human or animal travels. Attention has currently been driven towards this phenomenon as greater than 70% of the global population is no longer vaccinated against smallpox. Indeed, the smallpox vaccination also confers some indirect degree of protection against other poxviruses, including monkeypox. We performed a narrative review to describe existing literature with regard to monkeypox using MEDLINE, EMBASE and Scopus databases. This review aims to provide updated evidence of findings on epidemiology, clinical features, diagnosis, management, and prevention of monkeypox also considering the concurrent zoonotic pandemic caused by the coronavirus SARS-CoV-2.

Keywords: Monkeypox (MPX); epidemiology; zoonotic pandemic; smallpox

Citation: Di Gennaro, F.; Veronese, N.; Marotta, C.; . Title. *Viruses* **2022**, *14*, x. https://doi.org/10.3390/xxxxx

Academic Editor: Firstname Lastname

Received: date
Accepted: date
Published: date

1. Introduction

Monkeypox (MPX) is a viral zoonosis brought on by a double-stranded DNA virus. It is a member of the *Poxviridae* family and the orthopoxvirus genus, which also includes the smallpox virus known as the variola virus. [1]. The virus was initially discovered in monkeys at the Statens Serum Institute in Copenhagen, Denmark, in 1958 (1), giving rise to the moniker "monkeypox," while one Democratic Republic of the Congo children was the first cases discovered in 1970 [2]. There are two clades of monkeypox virus (MPXV): the West African, with an estimated case fatality ratio (CFR) less than 4% and higher prevalence in HIV patients, and the Congo Basin (Central African) with a CFR of 10% [2].

Historically, vaccination against smallpox had been shown to be cross-protective against MPX [3]. However, after the eradication declaration of smallpox in 1980 by the

World Health Assembly, vaccination against smallpox has ceased and acccording to estimates, more than 70% of people worldwide are no longer immune to smallpox.

Since 13th May 2022, many cases of MPX were reported from several non-endemic countries in Europe, North America and Australia [4]representing an unusual and alarming public health issue considering that it is not directly related to human or animal travels [5]. Indeed, the number of cases reported is surprisingly high, there is no direct link between outbreaks and travels from endemic areas, and it is not clear whether the virus has developed more capacity in transmission between humans and in general viral evolution and dynamics [6]. Also, despite the general low mortality rate and the fact that no death has been reported during the current outbreak, many unusual aspects are creating public concern.

Moreover, even if in recent years, there have been reported cases in non-endemic areas including the 2003 and 2021 outbreaks in the United States of America and Israel, the September 2018 outbreak in United Kingdom, and the May 2019 outbreak in Singapore, the current global epidemiology pattern has never been recorded before [7].

The MPV genomes are grouped into three monophyletic clades: two previously characterized clades (A.1 and A.2) and a newly emerging clade containing genomes from the ongoing multi-country outbreak in 2022 (B.1). Additionally, a recent article demonstrated the potential function of the enzyme APOBEC3 (host enzymes) in viral growth as well as in potential MPV adaptability in the course of microevolution by a detailed investigation of mutation hotspots.

Other articles have investigated how nine proteins could be crucial in the pathogenesis of the disease (A9L, A36R, A50L, B9R, B16L, C3L, C7L, C12L (SPI-1) and H5R) and four proteins are crucial for the host's immune response (A27L, A33R, B5R and L1R), bringing the scientific community's attention to their role in disease development and host protection.

It is therefore mandatory and urgent to increase the efforts to close the gap of scientific knowledge in order to stop current and future outbreaks and to optimize the surveillance and preparedness in containing and combatting MPX and zoonotic infections.

This review aims to provide updated evidence of findings on epidemiology, clinical features, diagnosis, management, and prevention of MPX also considering the concurrent zoonotic pandemic caused by the coronavirus SARS-CoV-2 that up until the end of June 2022, has caused almost 600 million COVID- 19 cases globally, with 6.3 million deaths [7]

2. Methods

We used the following search strategy in Pubmed ("monkeypox"[MeSH Terms] OR "monkeypox"[All Fields] OR ("monkeypox"[MeSH Terms] OR "monkeypox"[All Fields] OR ("monkey"[All Fields] AND "pox"[All Fields]) OR "monkey pox"[All Fields]) OR ("monkeypox virus"[MeSH Terms] OR ("monkeypox"[All Fields] AND "virus"[All Fields]) OR "monkeypox virus"[All Fields] OR "monkeypoxvirus"[All Fields]) OR ("monkeypox virus"[MeSH Terms] OR ("monkeypox"[All Fields] AND "virus"[All Fields]) OR "monkeypox virus"[All Fields]) OR ("monkeypox virus"[MeSH Terms] OR ("monkeypox"[All Fields] AND "virus"[All Fields]) OR "monkeypox virus"[All Fields] OR ("monkey"[All Fields] AND "pox"[All Fields] AND "virus"[All Fields]) OR "monkey pox virus"[All Fields]). The search was then adapted for Scopus for other relevant articles. We included all the observational and intervention studies including human beings having MPX as well as all kinds of reviews (Systematic and nonsystematic). Since a limited literature was anticipated, also case series,case reports, and pre-prints were considered.The search was updated up to 5th July 2022.

3. Epidemiology

In the Democratic Republic of the Congo (DRC), a 9-month-old kid was found to have the first human case in 1970 [8]. Since then, there have been more human MPX cases reported, with the DRC seeing the largest increase.

Before an epidemic of 47 confirmed or probable cases was reported in the US in 2003 as a result of exposure to infected pet prairie dogs that had contracted the MPX virus from infected exotic animals imported from Ghana, cases of MPX had only been recorded in Africa[9-10]. There have been several travel-related cases of MPX in recent years, all following exposures in Nigeria. In particular, in 2018 there was one case in Israel [11], three in the UK (two in 2018 [12], one in 2019 [13], and one in Singapore [14]. A fourth case was reported in the UK in 2018 as a result of nosocomial transmission to a healthcare worker [15].

To date MPX is endemic in the following countries: Benin, Cameroon, the Central African Republic, the Democratic Republic of the Congo, Gabon, Ghana (identified in animals only), Ivory Coast, Liberia, Nigeria, the Republic of the Congo, Sierra Leone, and South Sudan [16].

Data regarding incidence of MPX are extremely limited. One study conducted in the Democratic Republic of Congo reported that the incidence increased from 0.64/100,000 in 2001 to 2.82/100,000 in 2013. [17]. Moreover, another study carried out between 2005 and 2007 found that the average annual cumulative incidence of confirmed MPX from nine health zones in the Sankuru district was 0.55 per 100,000. [18]

Data on case fatality rate can be retrieved from a recent literature review that calculated a pooled estimate case fatality ratio (CFR) which was 8.7% across all countries [19].

However, of note all the deaths were observed in Africa [20]. In the same study, when the data were analyzed by clade, the CFR for the Central African clade (10.6%, 95% CI: 8.4–13.3%) was significantly higher than that of the West African clade (3.7%, 95% CI: 1.7–6.8%) [19].

Considering the demographic characteristics, males are more affected than females, and this condition primarily affects young people, despite the fact that the median age at presentation increased from 4-5 years in 1970-1989 to 10 years in 2000-2009 and 21 years in 2010-2019. [18-20]

4. Monkeypox multi-country outbreak, 2022

Between 1 January and 15 June 2022, 42 nations in five WHO Regions collectively reported 2103 laboratory confirmed cases, with only one death. [21]. Most cases (98%) documented since May 2022 have been found in men who have sex with men (MSM) seeking care in primary care and sexual health clinics, however this is not always the case. To yet, no travel connections to endemic regions have been discovered.

Up until July 05, 2022, 5949 cases of MPX had been identified across the European region via IHR mechanisms and official public resources from 33 countries. Of the 5266 cases reported in The European Surveillance System (TESSy), 5265 were laboratory confirmed, and 99 were confirmed to be of the West African clade where sequencing was available. The earliest reported date of symptom onset was April 17, 2022. The majority of cases were between the ages of 31 and 40 (2214/5258 - 42%) and male (5209/5230 - 99.6%). 40% (364/917) of cases with known HIV status were HIV-positive [22]. The majority of patients (2684/2793; 96.1%) had a rash, and 1931/2793; 69% had systemic symptoms such fever, exhaustion, muscular discomfort, vomiting, diarrhea, chills, sore throat, or headache [23]. There were no recorded deaths in any cases. [24]. Although some (15) instances involving health professionals were recorded, more research is being done to ascertain whether the infections were caused by exposure at work. [25]. Given the absence of epidemiological links to endemic areas, the unexpected appearance of MPX in several regions suggests that undetected transmission may have occurred for considerable time.

Pathophysiology and clinical manifestation

The MPX's natural reservoir has yet to be established, while rats are the most likely suspect. A possible risk factor is eating undercooked meat and other animal products from infected animals. People who live in or near wooded regions may be exposed to infected animals in an indirect or low-level manner. Although MPX is not easily transmitted, it can be transmitted through contact with contaminated body fluids or lesion materials, both directly and indirectly[26]. Direct exposure includes contacts to fomites, respiratory secretions or skin-to-skin contact with MPX patients. Being in the patient's room or within 6 feet of a patient while undergoing any treatments that might produce aerosols from oral secretions, skin lesions, or the resuspension of dried exudates without donning a N95 mask and eye protection can result in indirect exposure [27]. Transmission can also happen through the placenta (which can cause congenital MPX) or through intimate contact during and after child delivery.

After entry, the virus replicates at the inoculation site, first localizing in mononuclear phagocytic cells. Then, it is released into the bloodstream, and finally localizing again in skin cells. Following the first step replication, it spreads to local lymph nodes and, thus, provokes a viremia with 10 to 14 days (possible incubation period) [28]

The characteristic clinical manifestation consisting of vesiculo-pustular rash is usually preceded by prodromal non-specific symptoms as fever, chills, myalgia, headache, lethargy, and lymphadenopathy [29]. Importantly, patients are infectious starting from prodromal symptoms until lesions form scabs and scabs fall off. Usually, the oropharynx is the first site affected and then lesions appear on the skin.

The clinical presentation of MPX cases associated with the current outbreak has been variable thus far. Many cases in this outbreak do not exhibit the classically described clinical patterns for MPX (fever, swollen lymph nodes, followed by a centrifugal evolving rash). The presence of only a few or even a single lesion, lesions that start in the genital or perineal/perianal region and do not spread, lesions that manifest at various (asynchronous) stages of development, and the appearance of lesions before the onset of fever, malaise, or other constitutional symptoms are some examples of abnormal characteristics. [29,30]. The mechanisms of transmission during sexual contact remain unknown, despite the fact that it is known that close physical and personal skin-to-skin or face-to-face contact might result in transmission (through direct contact with infected skin).

Diagnosis and differential diagnosis

For the diagnosis, it is essential to first define 'suspect case' in accordance with WHO recommendations, i.e. a person of any age who presents in a non- MPX endemic country with an unexplained acute rash; and with one or more of the following signs or symptoms, for which the common causes of acute eruption do not explain the clinical presentation: headache, acute onset of fever above 38.5°C, lymphadenopathy, myalgia, back pain, asthenia [16]. In addition, many authors report a characteristic triad for the diagnosis of MPX: skin lesions, lymphadenomegaly, and fever [6,14].

For its specificity and sensitivity, the polymerase chain reaction (PCR) is the gold standard laboratory test, but the type and quality of the sample for the laboratory test is crucial. As a result, the best diagnostic samples for MPX are the fluid of vesicles and pustules, as well as dried scabs. Moreover, when it is possible, a biopsy may be utilized. As CDC recommendations, lesion samples must be maintained cool and stored in a dry, sterile tube [18].

Unfortunately, antigen and antibody detection assays do not offer MPX -specific confirmation because orthopoxviruses are serologically cross-reactive. When resources are limited, serology and antigen detection procedures are not recommended for diagnosis or case investigation. Furthermore, recent or past vaccine-based immunization may result in misleading positive findings. In addition, PCR on pharyngeal swabs and seminal fluid may be a good strategy considering the transmission pathways of the virus, especially if the patient presents symptoms such as sore throat or penile lesions.

As part of the clinical differential diagnosis, it is important to rule out other rash conditions such molluscum contagiosum, chickenpox, measles, bacterial skin infections, scabie's, syphilis, and medication-related allergies.

Lymphadenopathy can be used to differentiate MPX from chickenpox or smallpox during the prodromal stage of sickness. Additionally, non-infectious illnesses including Behcet's diseases, squamous cell carcinoma, and recurrent aphtous stomatitis must be ruled out in addition other MST (sexually transmitted disease) such as herpes simplex virus, syphilis, chan-croid, lymphogranuloma venereum (LGV), and granuloma inguinale are crucial in differential diagnosis [16,18]

Prevention and Treatment

Vaccination with first-generation (e.g. Dryvax, Aventis Pasteur Smallpox Vaccine), second-generation (e.g. ACAM2000) and third-generation (IMVAMUNE and LC16m8) vaccines is the first line of defense against orthopoxvirus disease. Despite the fact that these vaccines provide great protection, their widespread use is limited by the high rate of adverse events associated with live, attenuated virus immunization.

All first- and second-generation vaccines use live, replication-competent virus. A successful vaccination produces a lesion at the site of administration that generates infectious virus. However, there is risk of adverse events such as autoinoculation to other parts of the body as well as inadvertent transmission to other people, postvaccine encephalitis, and disseminated infection in immunosuppressed patients. The third generation vaccine no longer poses a danger of autoinoculation, unintentional transmission, or systemic dissemination, while having a greater safety profile due to its decreased capacity to replicate in mammalian cells and the absence of a lesion at the site of immunization. It is designated for people who have higher risk factors for adverse outcomes, such as people with HIV, hematological conditions, and immunocompromised individuals. [34-35]

There are no recognized treatment guidelines for MPX infection at this time.

Tecovirimat, a viral envelope protein p37 inhibitor that prevents virus particles from being released from infected cells, has been shown to be beneficial in treating a range of poxvirus-related illnesses in animal studies. It has been approved by the US Food and Drug Administration (FDA) for the treatment of smallpox since July 2018, and by the European Medicines Agency (EMA) for the treatment of MPX and cowpox since January 2022, despite the lack of clinical efficacy trials [31,32]. A very recent study on seven people with MPX in the UK in the 2018-2021 period showed good profile efficacy with Tecovirimat (ST-246) [33]. Currently Tecovirimat may be considered for treatment in people infected with: severe disease (e.g., hemorrhagic manifestation, CNS involvement, confluent lesions, sepsis) or in people with high risk of severe disease (people with immunocompromising conditions or pediatric populations, particularly patients younger than 8 years of age or pregnant or breastfeeding women).

Although there is inadequate data on their efficiency in treating MPX in humans, the antivirals cidofovir (CDV) and brincidofovir (BCV) might be utilized to treat MPX. These inhibit viral DNA polymerase and have variable degrees of effectiveness in treating various viral infections.

CDV and BCV have previously shown antiviral efficacy against adenoviruses and poxviruses, among other double-stranded DNA viruses. BCV is a lipid compound of the nucleotide analog cidofovir, also known as hexadecyloxypropyl-cidofovir [HDP-CDV] or CMX001 (CDV). BCV has a higher cellular absorption and greater conversion to the active form by intracellular enzymes than CDV.

Some studies have shown an interesting profile of BCV in animal models reducing mortality and risk of disease progression. In mice model, Brincidofovir (CMX001) and the smallpox vaccination can be given together without compromising immunity. [34]

Public health response

Although there are different hypotheses on how MPX reached non-endemic countries during the current outbreak [36], it appears to be spreading disproportionately through men who have sex with men (MSM) social networks [37,38]. However, the complexities of the current MPX outbreak in the context of non-endemic countries necessitate a comprehensive response that combines traditional public health countermeasures with risk communication and community strategies to engage diverse audiences based on the different risk of exposure, without stigmatization [38,39]

From a public health perspective, the priority should be to contain the virus spread. This could be achieved by implementing specific actions in both healthcare and community settings. In healthcare settings, increasing vigilance and clinical recognition of disease is essential to ensure early detection of cases, notification and isolation of patients. Healthcare human resources departments should be trained and equipped with all the diagnostic tools needed in order to make a timely diagnosis and isolation of suspected or confirmed cases with adequate ventilation, dedicated bathroom is strongly recommended. In the presence of a clinical picture that does not require hospitalization - if housing and hygiene conditions permit, the confirmed case may be followed at home according to locally defined procedures, in isolation also from cohabitants and any other caregivers.

Also, protecting healthcare workers and preventing transmission in healthcare settings (using PPE, following infection prevention and control procedures) should be guaranteed as soon as the outbreak is recognized. Healthcare workers caring for patients with suspected or confirmed MPX should implement standard, contact and droplet, precautions, both in outpatient and hospitals settings. Hand hygiene must be strictly followed, contaminated medical equipment must be handled with care, laundry and garbage must be disposed of properly, and environmental surfaces must be cleaned and disinfected.

In the community, in order to stop the chains of transmission, it would be important to intensify surveillance in specific population groups – such as MSM communities during the current outbreak -, along with case and cluster investigation and contact tracing activities. Indeed, surveillance and case investigation for MPX in the current context are essential to rapidly identify cases, clusters and sources of infection as early as possible in order to provide optimal clinical care, isolate cases to prevent further transmission, identify and manage contacts, adapt efficient control and preventive strategies based on the most often found transmission channels. Due to the hazards to the public health posed by even one MPX case, which is considered an outbreak itself in non-endemic countries, suspected cases should be reported to local and national health authorities immediately, regardless of whether other potential diagnoses are also being investigated. Cases should be reported as soon as possible, using the case definitions shared by public health authorities.

Surveillance of close contacts is also recommended; i.e., self-monitoring daily for the occurrence of signs/symptoms referable to MPX for a period of 21 days after the last contact with a patient or their contaminated materials during the infectious period. During the surveillance period, MPX case contacts should avoid contact with immunocompromised persons, pregnant women and children under 12 years of age and should not donate blood, cells, tissue, organs, breast milk or semen.

As for vaccines and immunization, although smallpox infection vaccines are thought to provide protection against MPX, using them during the 2022 outbreak is unlikely. Because of the cessation of smallpox vaccination programs over the last 50 years, as well as a lack of supply of effective vaccines, which are mostly only available in a few national stockpiles, these countermeasures, particularly suitable for contact prophylaxis, are not readily available in the short term.

Thus, implementing effective communication strategies should be a priority. Risk communication and community engagement are key measures. In fact, the primary preventative approach for MPX is to increase knowledge of risk factors and inform individuals of the steps they may take to lessen exposure to the virus.. Also, community engagement can help to avoid stigmatization of at-risk population groups and reduce impact on

societies and economics [40]. Public health authorities should always apply measures commensurate to the risk. At the current stage, international travel-related measures are not recommended but it could be important to promote safe mass gathering events in areas experiencing outbreaks [41]. In addition, public health containment measures, which are generally accepted in MPX endemic countries, may not be as well accepted in Western countries, especially after the Covid-19 pandemic. For example, a case of MPX school transmission, as recently observed in Quebec, may generate debate and difficulties for public health professionals that should be prevented by timely and specific institutional communication.

Learning from the COVID-19 pandemic, from a global perspective, governments, agencies, NGOs and industries should continue in the sharing of information, diagnostic resources and data as well as collaborate to ensure equitable access to countermeasures (vaccine, therapeutics, diagnostics) based on public health needs.

Strategies would also be to strengthen a "one health" approach in endemic countries, as environmental factors increase the frequency of contact with potential hosts, raising the risk of animal-to-human transmission.

5. Conclusions

This review gives readers insight into the current MPX scenario and paints a picture of the state of the art in terms of the influence on and reaction to public health, epidemiology, clinical features, diagnosis, management, treatment and prevention. Although MPX is not a new virus and has been causing regular outbreaks in poorer and remote areas in Central and West Africa, literature on this topic is limited. MPX is a perfect example of the potentially explosive mix of zoonotic spillover and anthropogenic drivers that accounts for the vast majority of the world's epidemic potential. Unlike other neglected diseases, we have options for treating and preventing MPX infection but access is challenging in that part of the world where it is most needed. Preparing for epidemics and global health requires responding to ongoing outbreaks where and when they occur, rather than waiting for them to spread elsewhere. However, the growing attention may contribute to better understanding of this infection and to the identification of the gold standard in terms of prevention, treatment and management but it will be important that each scientific progress and medical innovation can be accessible also to for those who can benefit the most. This is critical not only for equity, but also for global health security, because it is in everyone's best interest to solve a problem before it becomes a major one.

As for the current multi-country outbreak some challenges and open questions such as the unusually high number of cases in many countries in a short timeframe, the uncertainty about the future evolution, and the current limited existing medical countermeasures, still remains. Furthermore, since smallpox infection vaccines provide protection against MPX, and the vaccine is ready, we encourage the utilization of vaccines as soon as possible, at least for specific population groups and healthcare workers.

Finally, this outbreak is bringing back the spectre of the syndemic risk by the recent and ongoing Covid pandemic. Thus, it is mandatory to increase the efforts in order to block the infectious risk not only in the short term but in a long term and for all.

Author Contributions: Conceptualization,F.D.G., N.V.; D.P. and L.S; methodology, N.V. writing—original draft preparation, C.M.; F.V.S, A.Y.; A.S. M.B.; writing—review and editing, E.N.; Y.B.; A.S.; M.A.; P.S.; L.B.;C.P. All authors have read and agreed to the published version of the manuscript."

Funding: Please add: "This research received no external funding"

Institutional Review Board Statement: Not applicable

Informed Consent Statement: Not applicable

Data Availability Statement: Not applicable

Conflicts of Interest: The authors declare no conflict of interest

References

1. Petersen, E.; Kantele, A.; Koopmans, M.; Asogun, D.; Yinka-Ogunleye, A.; Ihekweazu, C.; Zumla, A. Human Monkeypox: Epidemiologic and Clinical Characteristics, Diagnosis, and Prevention. *Infect Dis Clin North Am.* **2019** Dec;33(4):1027-1043. doi: 10.1016/j.idc.2019.03.001.
2. Ogoina, D.; Izibewule ,JH.; Ogunleye, A.; Ederiane, E.; Anebonam, U.; Neni, A.; Oyeyemi, A.; Etebu, EN.; Ihekweazu, C. The 2017 human monkeypox outbreak in Nigeria-Report of outbreak experience and response in the Niger Delta University Teaching Hospital, Bayelsa State, Nigeria. *PLoS One*. **2019** Apr 17;14(4):e0214229. doi: 10.1371/journal.pone.0214229.
3. Simpson, K.; Heymann, D.; Brown, CS.; Edmunds, WJ.; Elsgaard, J.; Fine, P.; Hochrein, H.; Hoff, NA.; et al. Human monkeypox - After 40 years, an unintended consequence of smallpox eradication. *Vaccine*. **2020** Jul 14;38(33):5077-5081. doi: 10.1016/j.vaccine.2020.04.062.
4. Word Health Organization (WHO). Multi-country monkeypox outbreak in non-endemic countries. Available at https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON385 (last access 30 May 2022)
5. Word Health Organization (WHO). Multi-country monkeypox outbreak: situation update. Available at https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON393 (last access 06 July 2022)
6. Zumla, A.; Valdoleiros, SR.; Haider, N.; Asogun, D.; Ntoumi, F.; Petersen, E.; Kock, R. Monkeypox outbreaks outside endemic regions: scientific and social priorities. *Lancet Infect Dis*. **2022** May 27:S1473-3099(22)00354-1. doi: 10.1016/S1473-3099(22)00354-1. Epub ahead of print. PMID: 35636447; PMCID: PMC9141675.
7. Di Gennaro, F.; Petrosillo, N. New endemic and pandemic pathologies with interhuman airborne transmission through ear, nose and throat anatomical sites. Acta Otorhinolaryngol Ital. 2022 Apr;42(Suppl. 1):S5-S13. doi: 10.14639/0392-100X-suppl.1-42-2022-01
8. Breman, JG.; Kalisa-Ruti, Steniowski, MV.; Zanotto, E.; Gromyko, AI, Arita, I. Human monkeypox, 1970-79. *Bull World Health Organ*. **1980**;58(2):165-82. PMID: 6249508; PMCID: PMC2395797.
9. Yong , SEF.; Ng, OT.; Ho, ZJM.; Mak, TM.; Marimuthu, K.; Vasoo, S.; Yeo, TW.; et al. Imported Monkeypox, Singapore. *Emerg Infect Dis.* **2020** Aug;26(8):1826-1830. doi: 10.3201/eid2608.191387.
10. Beer, EM.; Rao, VB. A systematic review of the epidemiology of human monkeypox outbreaks and implications for outbreak strategy. *PLoS Negl Trop Dis.* **2019** Oct 16;13(10):e0007791. doi: 10.1371/journal.pntd.0007791.
11. Erez, N.; Achdout, H.; Milrot, E.; Schwartz, Y.; Wiener-Well, Y.; Paran, N.; et al. Diagnosis of Imported Monkeypox, Israel, 2018. *Emerg Infect Dis*. **2019** May;25(5):980-983. doi: 10.3201/eid2505.190076
12. Vaughan ,A.; Aarons, E.; Astbury, J.; Balasegaram, S.; Beadsworth, M.; Beck, CR.; Chand, M.; et al. Two cases of monkeypox imported to the United Kingdom, September 2018. *Euro Surveill*. **2018** Sep;23(38):1800509. doi: 10.2807/1560-7917.
13. Public Health England. Monkeypox cases confirmed in England – latest updates**.** Available from: https://www.gov.uk/government/news/monkeypox-cases-confirmed-in-england-latest-updates
14. Vaughan, A.; Aarons, E.; Astbury, J.; Brooks, T.; Chand, M.; Flegg P, et al. Human-to-human transmission of monkeypox virus, United Kingdom, October 2018. *Emerging infectious diseases.* **2020**;26(4):782.
15. Moore, M.; Zahra, F. Monkeypox. **2022** May 22. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022 Jan–.
16. European Centre for Disease Prevention and Control (ECDC). Risk assessment: Monkeypox multi-country outbreak. Stockholm: ECDC;23 May 2022. Available from: https://www.ecdc.europa.eu/en/publications-data/risk-assessment-monkeypox-multi-country-outbreak
17. Hoff, NA.; Doshi, RH.; Colwell, B.; Kebela-Illunga, B.; Mukadi, P.; Mossoko, M.; et al. Evolution of a disease surveillance system: an increase in reporting of human monkeypox disease in the Democratic Republic of the Congo, 2001–2013. *International journal of tropical disease & health*. **2017**;25(2). doi: 10.9734/IJTDH/2017/35885
18. Kugelman, JR.; Johnston, SC.; Mulembakani, PM.; Kisalu, N.; Lee, MS.; Koroleva, G.; et al. Genomic variability of monkeypox virus among humans, Democratic Republic of the Congo. *Emerging infectious diseases*. **2014**;20(2):232. doi: 10.3201/eid2002.130118.
19. Bunge , EM.; Hoet, B.; Chen, L.; Lienert, F.; Weidenthaler, H.; Baer, LR.; et al. The changing epidemiology of human monkeypox—A potential threat? A systematic review. *PLoS neglected tropical diseases*. **2022**;16(2):e0010141.
20. Nguyen, P-Y.; Ajisegiri, WS.; Costantino, V.; Chughtai, AA.; MacIntyre, CR. Reemergence of human monkeypox and declining population immunity in the context of urbanization, Nigeria, 2017–2020. *Emerging Infectious Diseases*. **2021**;27(4):1007.
21. Word Health Organitation (WHO). Disease Outbreak News 15 june 2022 https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON393
22. European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Monkeypox, Joint Epidemiological overview, 01 June, 2022.https://monkeypoxreport.ecdc.europa.eu
23. European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Monkeypox, Joint Epidemiological overview, 25 June, 2022. https://monkeypoxreport.ecdc.europa.eu
24. European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Monkeypox, Joint Epidemiological overview, 30 June, 2022. https://monkeypoxreport.ecdc.europa.eu
25. European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Monkeypox, Joint Epidemiological overview, 06 July, 2022. https://monkeypoxreport.ecdc.europa.eu

26. Nolen, LD.; Osadebe, L.; Katomba, J.; Likofata, J.; Mukadi, D.; Monroe, B.; Doty, J.; et al. Extended Human-to-Human Transmission during a Monkeypox Outbreak in the Democratic Republic of the Congo. *Emerg Infect Dis*. **2016 J**un;22(6):1014-21. doi: 10.3201/eid2206.150579. Erratum in: Emerg Infect Dis. 2016 Oct;22(10): PMID: 27191380; PMCID: PMC4880088.
27. Hutson, CL.; Carroll, DS.; Gallardo-Romero, N.; Drew, C.; Zaki, SR.; et al. Comparison of Monkeypox Virus Clade Kinetics and Pathology within the Prairie Dog Animal Model Using a Serial Sacrifice Study Design. *Biomed Res Int*. **2015;**2015:965710. doi: 10.1155/2015/965710. Epub 2015 Aug 24. PMID: 26380309; PMCID: PMC4561332.
28. Mucker, EM.; Chapman, J.; Huzella, LM.; Huggins, JW.; Shamblin, J.; Robinson, CG.; Hensley, LE. Susceptibility of Marmosets (Callithrix jacchus) to Monkeypox Virus: A Low Dose Prospective Model for Monkeypox and Smallpox Disease. *PLoS One.* **2015** Jul 6;10(7):e0131742. doi: 10.1371/journal.pone.0131742. PMID: 26147658; PMCID: PMC4492619.
29. León-Figueroa, DA.; Bonilla-Aldana, DK.; Pachar, M.; Romaní, L.; Saldaña-Cumpa, HM.; et al. The never ending global emergence of viral zoonoses after COVID-19? The rising concern of monkeypox in Europe, North America and beyond. *Travel Med Infect Dis*. **2022** May 25;49:102362. doi: 10.1016/j.tmaid.2022.102362.
30. Patrocinio-Jesus, R.; Peruzzu, F. Monkeypox Genital Lesions. *N Engl J Med*. **2022** Jul 7;387(1):66. doi: 10.1056/NEJMicm2206893.
31. U.S. Food and Druds. FDA approves the first drug with an indication for treatment of smallpox. Available at https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-indication-treatment-smallpox. Last access 5 July 2022
32. EMA (European Medicines Agency). Tecovirimat SIGA. Available at https://www.ema.europa.eu/en/medicines/human/EPAR/tecovirimat-siga. Last access 5 July 2022
33. Adler, H.; Gould, S.; Hine, P.; Snell, LB.; Wong, W.; Houlihan, CF.; Osborne, JC.; Rampling, T. Clinical features and management of human monkeypox: a retrospective observational study in the UK. *Lancet Infect Dis*. **2022** May 24:S1473-3099(22)00228-6. doi: 10.1016/S1473-3099(22)00228-6.
34. Parker, S.; Crump, R.; Foster, S.; Hartzler, H.; Hembrador, E.; Lanier, ER.; Painter, G.; et al. Co-administration of the broad-spectrum antiviral, brincidofovir (CMX001), with smallpox vaccine does not compromise vaccine protection in mice challenged with ectromelia virus. *Antiviral Res*. **2014** Nov;111:42-52. doi: 10.1016/j.antiviral.2014.08.003.
35. Hutson, CL.; Kondas, AV.; Mauldin, MR.; Doty, JB.; Grossi, IM.; Morgan, CN.; Ostergaard, SD.; et al. Pharmacokinetics and Efficacy of a Potential Smallpox Therapeutic, Brincidofovir, in a Lethal Monkeypox Virus Animal Model. *mSphere*. **2021** Feb 3;6(1):e00927-20. doi: 10.1128/mSphere.00927-20. Erratum in: mSphere. 2021 Feb 17;6(
36. Rizk, JG.; Lippi, G.; Henry, BM.; Forthal, DN.; Rizk, Y. Prevention and Treatment of Monkeypox. *Drugs*. **2022** Jun 28:1–7. doi: 10.1007/s40265-022-01742-y
37. Ferraro, F.; Caraglia, A.; Rapiti, A.; Cereda, D.; Vairo, F.; Mattei, G.; et al. Letter to the editor: multiple introductions of MPX in Italy from different geographic areas. *Euro Surveill.* **2022**;27(23):pii=2200456. https://doi.org/10.2807/1560-7917.ES.2022.27.23.2200456
38. 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. *Euro Surveill*. **2022;**27(22):2200421. https://doi.org/10.2807/1560-7917.ES.2022.27.22.2200421 PMID: 35656836
39. Minhaj, FS.; Ogale, YP.; Whitehill F. Monkeypox Response Team 2022. Monkeypox outbreak—nine states, May 2022. *MMWR* Morb Mortal Wkly Rep. **2022**;71:764-9. [PMID: 35679181] doi:10.15585/mmwr.mm7123e1
40. Daskalakis, D.; McClung, RP.; Mena, L.; Mermin, J. Centers for Disease Control and Prevention's Monkeypox Response Team*. Monkeypox: Avoiding the Mistakes of Past Infectious Disease Epidemics. *Ann Intern Med.* **2022** Jun 16. doi: 10.7326/M22-1748.
41. Di Giulio ,DB.; Eckburg, PB. Human monkeypox: an emerging zoonosis. *Lancet Infect Dis*. **2004** Jan;4(1):15-25. doi: 10.1016/s1473-3099(03)00856-9.
42. European Centre for Disease Prevention and Control/World Health Organization Regional Office for Europe. Interim advice for public health authorities on summer events during the monkeypox outbreak in Europe, 2022. 14 June 2022. Stockholm/Copenhagen; ECDC/WHO Regional Office for Europe: 2022. https://www.ecdc.europa.eu/en/publications-data/interim-advice-public-health-authorities-summer-events-during-monkeypox-outbreak