Journal of Ideas in Health

e ISSN: 2645-9248 Journal homepage: www.jidhealth.com Open Access

Review Article

Monkeypox in the COVID-19 era

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Abstract

Currently, in addition to the COVID-19 waves, the world is confronting an additional threat: the global monkeypox infection outbreak, already regarded as a “public health emergency of international concern” by the World Health Organization. According to the most recently published reports, more than 21000 monkeypox infection cases have been confirmed in 78 countries, with 5 African deaths and more than three deaths outside endemic Africa while the numbers are still increasing. Too little is currently known about the monkeypox virus, although it does not appear as a recently emerged pathogen, being probably as ancient as the smallpox virus. The major fear in regards to the current international monkeypox infection spread has multiple causes: monkeypox's similarity to smallpox, the deadliest pathogen in the history of humanity; lack of knowledge of the virus's natural occurrence, animal reservoir, mechanisms of transmission, pathogenicity, host immune response; lack of effective specific treatment and vaccine; unusually rapid geographic spread and atypical clinical presentation; increase in the mutation rate outside the standard, mathematically anticipated rates; putative complications and sequelae of the infection; potential use as a biological weapon. Actually, with such characteristics, the monkeypox virus has the potential to occupy/replicate the place of the much-feared smallpox virus. In the near future, due to the high registry of viral mutagenesis, limitations in the preventive strategies, and lack of an efficient vaccine, several viruses, including SARS-CoV-2 and monkeypox, could continue their worldwide spread and generate flu-like subsequent infective bursts. Therefore, dedicated research and detailed knowledge of the viral pathogenic mechanisms and transmission routes are required to design efficient therapies and limit/stop future pandemics: until the emergence of a new virus.

Keywords: Monkeypox, Smallpox, Variola Virus, Poxvirus, Vaccine, SARS-Cov-2, COVID-19, Outbreak, Epidemics, Pandemics, Romania

Background

Currently, along with the subsequent COVID-19 waves, the world is confronting a new threat: monkeypox infections, already declared a “public health emergency of international concern” by the World Health Organization (WHO) [1]. An apparently ancient zoonotic pathogen that is nowadays changing its biology, monkeypox is the isolated causative agent in more than 16000 new cases of infections worldwide in 2022, in 75 countries/areas (in the two Americas, Europe, North Africa, Middle East, Asia, Oceania, Australia) (even 21000 cases in 78 countries as reported by the BNO (BreakingNewsOn) on July 29, 2022) [1,2]. Therefore, the world is facing a monkeypox epidemic, with the potential of becoming a pandemic, as reported by the WHO [1]. It is already regarded as a global health problem, as it exhibits an unusual fast geographic spread, has the potential to occupy/replicate the ancient eradicated deadly smallpox place through evolutionary mutations, and there is no current efficient specific antiviral treatment, nor an ideal approved vaccine [3-6]. It is considered a High Consequence of Infectious Disease (HCID) in the UK and is treated in specially designated centers [7]. The monkeypox pathogen is a large (250 nm long and 200 nm wide), brick- or oval-shaped, lipoprotein-enveloped virus of approximately 200000 base pairs, consisting of a double-strand DNA, from the Orthopox genus, Poxviridae family, Chordopoxvirinae subfamily, with intra-cytoplasmic replication [3, 4, 6, 8]. Along with the monkeypox virus, the Poxviridae family includes multiple life-threatening viruses that can affect a broad array of organisms, humans or animals, such as human smallpox, that has been eradicated until 1980 (considered to

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have historically killed more than 300 million people), molluscum contagiosum virus, cowpox, rabbitpox, camelpox, mousepox (ectromelia virus), vaccinia and pox viruses affecting goats, cervids, rabbits, but even birds, reptiles such as crocodiles and insects [9-15]. There is a large degree of genetic similarity between the pox viruses, with highly conserved genes for virus replication and more variability in concern with the genes that dictate the host range, immune response, and pathogenicity [4, 10]. The most acknowledged and feared virus of the Poxviridae family is the smallpox virus, the deadliest human-specific virus ever described in the history of humanity. In fact, it is due to the historical smallpox epidemics that the vaccine and vaccination were invented and implemented for the first time by Edward Jenner due to the cowpox/vaccinia virus similarity to the smallpox virus [5, 15, 16].

The current preoccupation with the monkeypox virus: reasons for concern

In fact, the current fear in regards to monkeypox infections is determined by: its important similarity to the feared eradicated smallpox virus; significant lethality rates of up to 11%; potential use as a biological weapon; recent changing biology with the more frequent human-to-human transmission; rapid unexplainable geographic spread; atypical clinical presentation of the cases; unknown pathogenesis mechanisms; as well as due to the lack of an efficient and specific antiviral treatment for such a disease [6, 14, 17, 18, 19]. Too many unknowns are related to the monkeypox infection: the mechanisms of the natural occurrence of the virus; the routes of transmission are insufficiently studied and understood; the mechanism of human infectivity; the response of the human immune system to the virus; the histological changes within the human organs as a consequence of the infection; the short and long-term sequelae of the monkeypox infection [5, 6, 17, 18]. Detailed genetic knowledge of the monkeypox virus is also lacking, as the isolation and characterization of pathogens like smallpox and even monkeypox from ancient probes via molecular paleoepidemiology (ancient bones) has many limitations: difficulty in DNA isolation, purification, possible contamination of the genetic material from other sources (environmental or laboratory), a mixture of various DNA sources, partial damage of the DNA with time [20, 21]. However, in the absence of basic knowledge on the Monkeypox virus, efficient prevention of transmission and treatment of the disease is not possible in modern medicine. The current lack of knowledge and treatment of the Monkeypox infection can be explained by the relatively delayed isolation and description of the Monkeypox virus, although it is probably a persistent ancient pathogen, along with the smallpox virus. Actually, smallpox virus recordings date back from 1350 BC, with historical descriptions from the Egyptians and Hittites and periodical rebursts worldwide until its eradication [22]. However, the genetic and clinical similarity between the two viruses [17, 23, 24], the late discovery of the monkeypox virus, and the efficacy of the smallpox ring vaccination against monkeypox as well has probably led to a prolonged confusion between the two viruses, with historical monkeypox infections misdiagnosed as smallpox cases, the monkeypox virus not being known at that time. Only after the smallpox eradication (due to the large-scale worldwide ring vaccination program), as officially declared in 1980 and after the cessation of the vaccination campaign, has the Monkeypox virus existence become obvious to the medical community [5, 15, 18, 22, 25, 26].

First isolation and history (transmission routes)

The monkeypox virus was first described only in 1958 by the Danish virologist Preben Christian Alexander von Magnus, being isolated from a group of monkeys that had been shipped from Singapore to Denmark to be used for polio vaccine [3, 5, 20, 27-30]. At that time, it had been considered as affecting only animals, with a reservoir in the central and western African rain forests. The first case of monkeypox infection in humans was recorded in 1970 in a 9-year child from Zaire, the current Democratic Republic of Congo, who was first suspected of smallpox infection but tested positive only for monkeypox virus [4, 12, 20, 23, 28, 31]. The recognition of the monkeypox infection is most probably due to the smallpox eradication and cessation of the vaccination program [32] and not to the monkeypox infection emergence at that time. However, monkeypox has been long regarded as a zoonotic infection, with a persistent African animal reservoir and only rare animal to human transmission. In fact, the exact African animal reservoir is still largely unknown [6, 10, 18, 24]. Although the infection bears the name "monkeypox", it is nowadays acknowledged that it is not the Monkeys that are the common natural reservoir for such a viral transmission and that monkeys are only an incidental host, along with many others and humans [4, 5, 20, 25]. In fact, repeated infective studies using various species of monkeys and rodents have shown that some species can even be immune to the infection (do not develop the disease or show an atypical, subclinical course of the infection). However, rhesus macaques appear to be susceptible to it, with lethality rates of up to 80% after intravenous injection of high doses of Monkeypox virus, although the natural transmission route is not intravenous [10, 14, 17, 33]. That is the argument that led to the recent proposal of renaming the virus, with the exclusion of the term “Monkey” [34]. Instead, the natural reservoir for the Monkeypox virus is considered to be several African rodents, such as giant pouched rats, dormice, rope squirrels, and tree squirrels, although precise data on this matter are currently lacking [4, 12, 20, 29, 32]. In the central and West African rain forests, where monkeypox infection is endemic, an important transmission route of the virus appears to be from animal to human due to the direct contact with live animals or carcasses, scratches, bites, skin lesions caused by rodents to humans, contact with animal saliva, respiratory droplets or skin lesions, frequently occasioned by hunting and animal skinning and even consumption of inadequately cooked bush meat [4-6, 12, 15, 24, 28, 29]. However, an additional transmission route has also appeared obvious: human-to-human transmission, mainly among household members or in hospital settings [7, 12]; such a transmission route requires direct, intimate contact, in contrast to the much more infective SARS-CoV-2 virus [35-37].

Although monkeypox infection is regarded as endemic in Africa, viral outbreaks outside the African continent have been rare. For example, in 2003, there was a monkeypox outbreak in humans in the United States, linked to the adoption of prairie dogs that got infected by exotic African Gambian giant rats and other rodents imported from Ghana. At that time, 72 human

cases of Monkeypox infection were recorded [29], all linked to contact with the infected exotic rodents shipped from Ghana to the United States [3, 6, 12, 25, 29]. Since then, the number of non-African monkeypox infection cases has increased worldwide, initially with occasional reports in the UK, Israel, the US, and Singapore, mostly linked to travel to the African continent and household interactions [7, 8, 18, 23, 25, 30]. However, from its first human description until now, probably due to the wane in the immunity conferred by the smallpox vaccine, especially in the young, non-vaccinated individuals, there has been a gradual increase in the number of monkeypox infections as reported by the African countries [4, 6, 11, 12, 16, 23, 25, 29, 38].

Current Out-African monkeypox outbreak

Nowadays, however, starting with the end of April and the beginning of May 2022, we are facing an unusual, unexpected out-African outbreak of monkeypox infections worldwide, with mysterious/undocumented and difficult to understand links for such a large geographic spread. In the current outbreak, no apparent links between most of the cases of monkeypox infection could be found [38]. Actually, a recent theory for the current extended geographic spread of the monkeypox virus suggests that the medical attention and resources focused on COVID-19 could have led to poorer monkeypox surveillance, diagnosis, and prevention [4]. Some reports link the current monkeypox infection outbreaks to LGBT/MSM (men having sex with men) prides, various festivals, and events that gather many people, such as the recent Gay Pride Maspalomas from Gran Canaria Island, as the majority of the infected cases were declared to be MSM (men having sex with men) individuals [6, 8, 28].

According to the WHO report, as of July 25, 2022, 16016 cases of infection and five deaths (in Africa) were confirmed in 75 countries/areas worldwide [1]. About 98% of the cases that reported their sexual orientation were gay or bisexual, and more than 41% of the documented cases were HIV-positive [1, 28]. According to the European Centre for Disease Prevention and Control update, as of August 08, 2022, there were 13912 confirmed cases of Monkeypox infection in 29 EU/EEA countries [39]. According to the BNO (Breaking News) news, on July 29, more than 21000 cases in 78 countries worldwide have been reported [2]. Five deaths in Africa have been recorded [40]. Up to now, the countries with the largest number of Monkeypox infection cases are: Spain, the US, Germany, the UK, France, Netherlands, Portugal, Italy, Belgium, and Austria, but the situation can change rapidly [1, 6, 25, 38]. Also, 37 countries have recently reported a weekly increase in the number of Monkeypox infection cases, according to the WHO report published on July 25, 2022 [1]. In fact, Belgium is the first country to introduce a 21-days mandatory quarantine for Monkeypox infection cases [6, 28]. More than three deaths outside of Africa (from Spain and Brazil) have already been recorded [41, 42].

Actually, it can be speculated that a monkeypox infection outbreak in non-endemic areas could lead to more severe consequences, as there is no pre-existing anti-poxvirus immunity in the countries outside endemic Africa [15]. Along with the smallpox vaccine waning immunity, vaccination cessation, and COVID-19 attention-shift, other putative mechanisms to explain the current monkeypox worldwide spread are: the extension of urbanization, deforestation and climate changes with the alteration of the wildlife habitat, increasing animal-to-human interactions; extensive hunting with bush meat consumption and worldwide exotic animal trade; increase in the percent of the immunocompromised population (HIV-positive individuals) and increase in the number of LGBT parades [4, 18, 23, 28].

Human-to-human monkeypox virus transmission mechanisms

In Africa, two major viral clades are the western and the central clade (from the Congo basin). The geographic region between the Cross and the Sanaga rivers has probably acted as a barrier to viral propagation, leading two the occurrence of two different viral clades [28, 32]. The central clade of Monkeypox virus is characterized by a higher aggressiveness and infectivity than the western clade, being responsible for a fatality rate of up to 10-11%, while the west clade associates lower fatality rates of 1-3% [3, 4, 7, 12, 18, 28]. Fortunately, the current worldwide outbreak appears to be a western clade Monkeypox transmission [7, 25]), with 0% fatality [28] or a low rate of fatality as reported until now by the WHO and the European Centre for Disease Prevention and Control [1, 39-42].

It is clear now that human-to-human transmission requires close/prolonged contact between individuals, such as interactions between household members, sexual contact, or healthcare professionals' interaction with Monkeypox-infected patients. Currently, the studies are insufficient, and debates persist on the human-to-human transmission mechanisms. However, it appears that the human-to-human transmission is possible via close (and usually prolonged) contact with body fluids and skin lesions such as: by large respiratory droplets while sneezing and coughing; direct contact with the Monkeypox skin lesions of an infected individual, or indirect contact with skin lesions material via bed linen, towels, contaminated clothes, various surfaces touched by an infected case and contaminated; putative contact with infected blood/urine/other body fluids, even feces [3, 4, 11, 25, 29, 32, 38].

Another transmission route can be via the placenta [6, 32]. A controversial spread of the infection is the sexual transmission route, either by the intimate contact with the skin lesions of the partner/ respiratory droplets and/or even by the seminal/sexual fluids, where the Monkeypox virus has been isolated in large titers, comparable to those of the nasal/throat swab titers [8, 28, 32, 38]. However, the sexual transmission route via seminal fluids remains much disputed [6]. Some authors, even if acknowledging that the Monkeypox virus, along with other sexually transmitted viruses, is present in the semen, doubt the viral transmission via such a route. They consider that the monkeypox virus high titers in semen are only secondary, via the systemic viral spread during the infection, especially in immunocompromised individuals, due to the permeability of the blood-testis barrier and the viral immune escape at that level, the testis being considered an immunologic “sanctuary site” [8, 28]. However, more than 50% of the cases of the current worldwide outbreak were among MSM, with past or current history of other sexually transmitted infections as well (HIV, hepatitis B or C, syphilis, herpetic, chlamydia infections)

having an atypical presentation with primary genital/perianal lesions and inguinal lymphadenopathy a short time after non-protected sexual contacts; another unusual presentation of such cases was with genital lesions only [6, 8, 25, 28, 38]. Such a fact clearly suggests that the sexual route is a major transmission route for the Monkeypox infection and that the genitals could represent a monkeypox virus reservoir [7].

Additionally, to the mentioned transmission mechanisms, if we consider the monkeypox similarity to the smallpox virus, other putative feared transmission routes can be taken into consideration, such as long-distance aerosol convection dissemination, as reported for the variola virus [43]. Such a transmission route could explain the current rapid geographic spread of Monkeypox infections worldwide, with no apparent links between many of the cases. The highest risk of monkeypox infection is among the individuals that have not been vaccinated against smallpox, with immune vulnerability: children, young individuals, pregnant, elderly individuals; immunocompromised individuals, HIV patients, patients with other sexually transmitted infections that may act synergically; certain professional categories, such as healthcare providers and animal trade professionals [4, 7, 8, 12, 24-26]. In fact, it was reported that adult laboratory animals such as Mus Musculus with a healthy immune system remain resistant when challenged to monkeypox virus [5], while a deficient immune response favors the infection [14]. Another category of individuals at risk are obviously those that undertake risky sexual behavior, with non-protected sexual intercourse, multiple, frequently anonymous partners, especially among the MSM, and those with other sexually transmitted diseases, that are also frequently vulnerable to infection due to their immunocompromised status [38]. Instead, older people that have been vaccinated against smallpox do not develop the disease or present only with mild forms of monkeypox infection, the smallpox vaccine being considered protective in 85% of the cases, even after more than 25 years from the vaccination [4, 12, 16, 25].

Clinical presentation of the monkeypox infection

The incubation of the monkeypox virus ranges from 5 to 14 days and even up to 21 days post-exposure [25, 32]. Although detailed medical data on the pathogenesis of the infection and host immune response are currently lacking, the clinical presentation of the monkeypox infection has the following stages: a prodromal, flu-like manifestation characteristic of the invasion period lasting up to 5 days, with fever, chills, headache, backache, myalgia, fatigue, asthenia, sore throat, arthralgia, when the systemic viral spread takes place; the virus is most likely taken up by lymphocytes/immune cells to the lymph nodes and other immune organs (spleen or even bone marrow), a phase that is characterized by lymphadenopathy, especially inguinal and cervical and less frequently axillary lymphadenopathy; 1-3 days after the prodromal stage with lymphadenopathy or sometimes even concomitant with the characteristic monkeypox infection rash appears [4, 6, 12, 28, 29, 32]. Typically, there is a monomorphic centrifugal skin eruption, with the progression of skin lesions from macules to papules, then pustules, umbilicated pustules, ulcerations, crusts, and scars over approximately 2-4 weeks. Usually, the skin eruption is located on the face (in 95% of the infected individuals), extremities (palms of the hands, soles of the feet, arms, legs), but also affects the mucous membranes (starting with the oropharynx, nose), conjunctivae, genital organs [3, 6, 28, 29, 32]. The skin lesions are firm, well-circumscribed, deep, 2-10 mm in size, and can be present in small numbers or up to thousands, usually in crops [3, 12, 25]. The infection is usually mild and lasts 2 to 4 weeks.

The healing is natural, spontaneous, and without additional medical intervention (self-limited infection) [25, 32]. The individuals are usually considered infective until the crusts fall off (the desquamation lasts between 7 to 14 days) [3]. However, reports on monkeypox virus isolate in upper respiratory tract swabs/other body fluids even after skin lesions resolution can suggest a longer contagious period [7]. It is not known for how long the contaminated materials/crusts could contain viable viruses in the environment and the precise duration of the infectivity period [7]; however, it was reported that the variola virus could remain viable and be isolated up to 13 years in the skin crusts kept at room temperature [43]. Also, there are reports of recurring diseases [7]. However, rarely, depending on the viral clade, infective dose, host immune system, and comorbidities, there can also be complications and sequelae, such as pneumonia, encephalitis, secondary bacterial infections, sepsis, sight-threatening lesions, vision loss, azoospermia, miscarriage (pregnant patients), permanent pitted skin scars (the most frequent sequelae), skin hyper- or hypopigmentation, skin bacterial superinfections, and death (1% to 11% mortality rates) [3, 7, 9, 12, 23-25, 28, 44].].

Monkeypox infection case definitions

There are two recent Monkeypox case definitions in the current literature: the Portuguese Directorate-General of Health definition of a suspected, probable, and confirmed case; and the Bunge et al. definition of a monkeypox case [23, 28]. Other definitions were proposed and used across time as well, such as that of the DRC (Democratic Republic of Congo) Ministry of Health in endemic areas [24], but an update on the definition of monkeypox cases is much needed [23, 28]. According to the Portuguese definition, starting with March 15, 2022, a suspected case is an individual that presents with localized or generalized skin eruption (rash) at any stage/anogenital lesions and one or more of the prodromal symptoms (high fever, more than 38 Celsius degrees; headache; backache; myalgia; asthenia; lymphadenopathy), after excluding other sexually transmitted diseases and other differential diagnoses. A probable case has been added to the suspected case contact with a monkeypox case within 21 days from the first symptoms, either by direct contact, sexual contact, hospitalization, or travel to monkeypox-endemic areas. A confirmed case means a laboratory-proven infection [28, 38]. The laboratory diagnostic of the monkeypox infection can be done by PCR (polymerase chain reaction), Western blot, positivity for IgM antibodies (ELISA), virus isolation and culture, immunohistochemistry, using material/fluid from the skin lesions, blood, and other body fluids of an individual [4, 6, 7, 12].

The differential diagnosis for monkeypox infection

Due to the skin rash that is associated with monkeypox infection, several differential diagnoses can be considered, including multiple sexually transmitted infections: smallpox

(historically); HIV-associated dermatitis; syphilis; herpetic lesions; varicella, scabies, rickettsia pox, generalized vaccinia, bacterial infections, and even drug-associated skin lesions [3, 11, 12, 28]. The lymphadenopathy is the key finding that differentiates the Monkeypox infection from smallpox, as otherwise, the clinical presentation of the two is indistinguishable [9, 11, 16, 24]. However, the current 2022 outbreak is characterized by an atypical presentation, most likely linked to the sexual transmission of the virus, with anogenital, even lower abdomen lesions; primary skin eruption on the thigh; pleomorphic erosions (simultaneous occurrence of various development stages of skin lesions, such as maculo-papules, pustules, crusts, and scabs); inguinal lymphadenopathy; and change in the onset from childhood to a mean age of thirties [7, 23, 28, 45].

The atypical presentation of the monkeypox infection appears to be determined by the recent mutations of the virus. Historically the Monkeypox virus, like other DNA viruses, has been relatively well conserved genetically but with potential for evolutionary mutations via subsequent selections [20]. However, lately, some authors have described an atypical, mathematically unanticipated number of mutations (10 times more than the usual mutation rate) that appear to be responsible for a more effective human-to-human transmission, increase in the monkeypox infection incidence, atypical clinical presentation, modified course of the disease and host immune modulation/escape [4, 6, 11, 18, 20].

Lack of sufficient current knowledge on the two similar viruses: smallpox and monkeypox

Smallpox was the most deadly virus in the history of humanity. However, as it was officially declared eradicated in 1980 when there were no modern virological, immunological, or histological techniques, our medical knowledge of it is reduced to the clinical and dermatological descriptions of those times. A more detailed description of the pathogenesis of the virus would have helped us with the understanding of the Monkeypox virus infectivity, as the two viruses share many similarities [5, 12, 15].

Unfortunately, knowledge of the monkeypox virus is also scarce, and most of the data come from recent animal models of macaques or rodents infected with monkeypox or vaccinia virus to study smallpox. The smallpox virus has been eradicated, but due to a fear of a biological threat, there are still two variola virus stocks kept in maximum containment facilities: CDC (that is, US Centers for Disease Control and Prevention) in Atlanta and Vektor, located in Russia, Novosibirsk, under the surveillance of the WHO biosafety experts [16, 22]. That is, most of the monkeypox studies have been conducted until the current outbreak due to a persistent preoccupation with a potential bioterrorist threat with the smallpox virus [46, 47] and are not necessarily directly linked to the monkeypox virus per se [16, 29, 33, 48]. However, smallpox studies on humans are impossible due to ethical issues and putative severe health consequences for the subjects. Therefore, most of the studies were smallpox surrogates using animal models of monkeypox virus infection [4, 19, 48]. Still, the current worldwide monkeypox infection outbreak clearly highlights the paucity of data on monkeypox transmission routes, pathogenesis, host immune response to the virus, and lack of specific treatment for it. Despite the clinical description, there are no specific studies to describe the detailed biochemical, molecular, histologic, and immunologic changes that occur during and after the infection, nor post-mortem descriptions. Also, information on the monkeypox virus's natural occurrence and transmission routes is insufficient, even in endemic areas [4].

The paucity of data on the biochemical, pathologic, and immunologic changes that occur during monkeypox infection

Despite the loud clinical presentation, the only biochemical changes reported by a few authors are inconsistent, such as lymphopenia, hypoalbuminemia, increases in the C-reactive protein and alanine transaminase (ALT) levels, and only rarely increased BUN (blood urea nitrogen), creatinine levels, anemia or thrombocytopenia; also, limited reports on cytokine level changes in macaques models of monkeypox infection, such as increases in the IFN-γ, IL-6, IL-8 IL-1ra [7,9, 45, 48]. Other blood parameters, including ferritin or other inflammatory/immune markers as measured in the case of COVID-19 [49], have not been analyzed yet in monkeypox patients. Also, the mechanisms of immune response to the Monkeypox virus remain elusive. However, the Monkeypox virus appears to ensure its spread to the lymphatic organs and blood and afterward to multiple organs such as the skin, respiratory system, digestive tract, testis, and less frequently to the liver, kidney, and bone marrow, via the lymphocytes that take up the pathogen. Afterward, the virus has multiple cytopathic effects, leading to inflammation, promoting cell apoptosis or necrosis and ulceration, as described in animal models of monkeypox infection [48].

Most of the more detailed tissue and organ lesions are known due to the animal models used to study the infection. The effects seen in the superficial skin are cell ballooning, necrosis of the keratinocytes, ulcerations, and hyperplasia; in the derma: inflammation with an initial lymphocytic infiltrate, followed by neutrophilic, eosinophilic, macrophage, and multinucleated giant cells infiltrate; vasculitis; in the lymph nodes: hyperplasia with lymphadenopathy; spleen and tonsil lesions; in the digestive tract: vesicles, pustules, ulcerations leading to dysphagia, nausea/emesis and even diarrhea leading to dehydration; respiratory tract: ulcerations, with pharyngitis, laryngitis, bronchitis, pneumonitis; conjunctivitis and sight-threatening lesions; potential to cause orchiepididimitis with fibrotic and azoospermia sequelae, similar to the smallpox infection; rarely, it can cause even hepatitis or nephritis, heart and brain lesions [8, 10, 12, 25, 33, 48].

Such advanced cytopathic effects with putative sequelae can be partly explained by the central clade viral ability to block and evade the immune system mechanisms, such as the complement system, T-cells, and NK lymphocytes, inhibition of inflammatory cytokine generation, decreased NK cell chemokine receptor expression, migration capacity, and killing function, loss of cytokine secretion and immune cell degranulation functions. In this context, multiple immunomodulatory mechanisms have been described for central clade monkeypox virus: complement system inhibition via complement control protein homologs; acquisition of host immune system evasion genes; interference with the T cell receptor-mediated T–cell activation by the central monkeypox

clade; suppression of the T-cell functions; inhibition of the complement enzymes; prevention of the transcription of the host immune system genes and even expression of an antibody-dependent enhancement of infection [4, 6, 12, 17, 50], as in COVID-19 [36, 51]. For variola virus and other poxviruses, a homologous IL-18 (interleukin 18) binding protein neutralizing human IL-18, important in the evasion from the host immune response, has been described [46] and remains to be investigated in monkeypox virus as well.

Prevention and treatment

Although the smallpox vaccine could be reintroduced, the interruption in its routine administration was due not only to the smallpox eradication but also to the important adverse effects of the vaccine, especially of the live variants, with cases of significant skin scars, post-vaccinal encephalitis, variolization/generalized vaccinia, myopericarditis, cardiac arrhythmias, sepsis and even death [16, 19, 24, 29]. However, fortunately, there are no smallpox alive, fully replicative vaccines in use for monkeypox prevention/treatment [4, 12]. Nowadays, among the various smallpox vaccines, there are two types regarded as safer (although none of them is ideal) available in the US that could be offered to monkeypox contacts and healthcare providers for preventive reasons or to ease and shorten the course of the disease: JYNNEOUS and ACAM 2000 (Imvanex and Imvamune) which are live, attenuated, non-replicating vaccinia virus Ankara strain, which require two doses. JYNNEOS vaccine is considered safe even in immunocompromised individuals and cases of atopy [3, 4, 12, 25, 26, 38]. For prophylactic reasons, the vaccine must be delivered ideally within four days post-exposure and maximally (but not proven effective) within 14 or even 21 days after the exposure to the virus [3, 7, 29). However, none of them is considered ideal, nor has it been designed specifically for monkeypox. There are also two antiviral treatments: Brincidofovir, designed for cytomegalovirus retinitis in HIV patients, which is an antireplicative drug; ST-246, later known as tecoviramat, designed for smallpox treatment (as an anti-cowpox virus replication drug), blocks the release of the virions from the infected cells [4, 12, 25]. Tecoviramat has already been approved for monkeypox infections but is not available worldwide [32]. Another option is the prophylactic intravenous administration of vaccinia immune globulin, but its usefulness has not been sufficiently explored yet [25].

Currently, it becomes obvious that there is a significant registry of information on SARS-CoV-2, which is a recently described virus, while the comparatively ancient monkeypox virus is insufficiently studied. Such a contrast is due to the distinct historical timing of the emergence of the two viruses, with totally different medical research availabilities. However, even for the much-studied SARS-CoV-2, the pathogenic mechanisms and mechanisms of propagation across species are insufficiently understood [36, 52, 53]. Nonetheless, the preoccupation with the Monkeypox virus will gain place due to its fast geographic spread and already reported deaths outside of Africa, but also because a lot of attention is paid to the exterior aspect, such as skin scars. As nowadays monkeypox infection is a recognized global health problem, with potential to become a pandemic, while the world is still vulnerable due to the COVID-19 repeated waves, multiple preventive strategies are to be considered: avoiding contact with infected patients or suspected cases that present with fever and rash; isolation/quarantine of the confirmed cases and of the contacts, ideally in negative-pressure rooms; manipulation of the personal objects (linen, towels) of the infected patients with gloves and careful disinfection of the laundry; vaccination and/or antiviral drugs; vaccination and professional protective equipment for the healthcare providers including N95 mask, protective eyeglasses/eye protection, gloves, gown; good hand hygiene; educational programs for the general population (reeducation of the population towards an adequate hygiene), as the level of knowledge on monkeypox disease is still low; specific education for the individuals that have high-risk sexual behavior; restriction of exotic animal trade; immediate quarantine of the animals suspected to be infected; prevention of unprocessed meet consumption in endemic countries; adequate epidemiological control with the identification of clusters and gathering of information from festival/event's organizers [3, 25, 30, 32, 38, 54].

Conclusions

However, with the COVID-19 pandemics, it has become obvious that no virus can be contained, and sole isolation/quarantine [53, 55-57] can bring only disastrous economic and social effects. Also, a ring vaccination, as in the case of smallpox, is no longer possible because people cannot be forced to be vaccinated, due to the lack of an ideal efficient vaccine, especially for patients with vulnerable immunity (children, pregnant, elderly, immunocompromised), the impossibility of geographically tracing all contacts with the progress of fast transportation means across the globe and the persistence of the animal reservoir. In the near future, due to the high registry of viral mutagenesis, we can expect that viruses such as Monkeypox and SARS-CoV-2 will continue their worldwide spread and generate flu-like subsequent infective bursts. Only detailed knowledge of the viral pathogenesis will make possible a decisive cure and cessation of such epidemics /pandemics: until the emergence/reemergence/discovery of a new virus. Therefore, all efforts should be conducted towards specific, dedicated studies to understand the pathogenic mechanisms of such viruses that are essential to design an effective treatment if we want to survive the next wave.

Abbreviation

WHO: World Health Organization; BNO: BreakingNewsOn; MSM: Men Having Sex With Men; HIV: Human Immunodeficiency Virus; The DRC: The Democratic Republic Of Congo; SARS-Cov-2: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19: The Coronavirus Disease 19; DNA: Deoxy Nucleic Acid; PCR: Polymerase Chain Reaction; ELISA: Enzyme-Linked Immunosorbent Assay; CDC: US Centers For Disease Control And Prevention; ALT: Alanine Transaminase; BUN: Blood Urea Nitrogen; IL: Interleukin; IL-6: Interleukin 6; IL-8: Interleukin 8; IL-18: Interleukin 18; IFN-Gamma: Interferon-Gamma; HCID: High Consequence of Infectious Disease.

Declaration

Acknowledgment

None.

Funding
The author received no financial support for the research, authorship, and/or publication of this article.

Availability of data and materials
Data will be available by emailing angelalazar.2008@yahoo.com.

Authors' contributions
Angela Madalina Lazar (AML) is the principal investigator of this manuscript (Review Article). AML is the author responsible for the study concept, design, writing, reviewing, editing, and approving of the manuscript in its final form. AML has read and approved the final manuscript.

Ethics approval and consent to participate
We conducted the research following the Declaration of Helsinki. However, Review Articles need no ethics committee approval.

Consent for publication
Not applicable

Competing interest
The authors declare that they have no competing interests.

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Article Info
Received: 31 May 2022
Accepted: 12 August 2022
Published: 17 August 2022

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