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Update on Monkeypox Virus Infection

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ABSTRACT

The World Health Organization declared the 2022 Monkeypox outbreak as a Public Health Emergency of International Concern, reflecting the rapid spread of infections in non-endemic countries. Since 2022, more than 95,000 confirmed cases with 185 deaths were reported in at least 117 countries, most of them in Europe and USA. Gender-based studies documented preponderance in men (96.8%). Most of them were men who have sex with men (MSM) suggesting the sexual route as the main way of transmission. Mpox infection is usually transmitted by close contact through body fluids, and genital secretions. Exposure to infected respiratory droplets occurs after prolonged exposure. Indirect contact is less frequent. Incubation period is in average 12 days. Prodromal symptoms are systemic and nonspecific succeed with lymphadenopathy. Eruptive rash is changing from macules-papules-blisters-pustules to scabs. Diagnosis is based on clinical occurrence of typical skin and/or mucosal lesions, systemic symptoms, and potential contact to a Mpox-infected individual. The preferred diagnostic test is real-time or conventional polymerase chain reaction (PCR). Laboratory tests based on the detection of antigens or antibodies are not used due to serological cross-reactivity with other orthopoxviruses. The world health authorities agree that smallpox vaccines protect against Mpox infection due to the antigenic similarity between both viruses. New vaccine approved is MVA-BN which contain an attenuated form of vaccinia virus "Ankara" related to the smallpox virus. Antivirals are used to treat Mpox infection, namely cidofovir, tecovirimat and brincidofovir. Individual and universal protective measures should be used to prevent the spread of Mpox viral infection.

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Monkey poxvirus (Mpox) infection is a zoonotic disease with occasional outbreak in endemic countries in West and Central Africa. Since early May 2022, multiple cases and clusters were reported from countries where the disease is not endemic and at the same time also in endemic countries showing widely disparate geographical areas. Mpox was first identified, and outbreaks were usually reported from West and Central Afrika, although small numbers of cases were traced to travel from these countries elsewhere. In 2022, most cases from non-endemic countries reported travel history to countries in Europe and North America, rather than to West or Central Africa. World Health Organization (WHO) has been collaborating with health authorities in affecting countries and prepared a program how to stop the rapid spread of infection in non-endemic countries. On July 23. 2022, WHO declared the 2022 monkeypox outbreak as the Public Health Emergency of Internal Concern". Periodical surveillance of Mpox infection is recorded from all affected countries worldwide to the WHO and monthly publications show the current data on the WHO websites. On May 31. 2024, the last update released the data from April 2024, declaring the total confirmed 95,226 cases have been diagnosed across 117 countries and 185 deaths were reported globally. These data declare that Mpox infections represent a moderate global risk [1,2].

Many causes could be responsible for the current unprecedented explosion of Mpox cases including changes in viral microevolution, connected with human interventions such as deforestation or climate changes. It is believed, that Mpox virus have been originated in the rainforests of the West and Central Afrika, where the Mpox virus has animal reservoirs. Close contact of humans in this area with forests or consuming wild animals are thought to be predictive for crossing the species barrier. On the other hand, the cessation of smallpox vaccination in 1980 may also play very important role. More than 90% of all Mpox cases were young people who have not been vaccinated because of the stoppage of the routine smallpox vaccination program [3].

The history of Mpox viral infection started in 1958. The Mpox virus was identified in two colonies of monkeys (crab-eating macaque) shipped from Singapore to a research facility in Copenhagen. The first human case of Mpox was documented in the Democratic Republic of Congo in 1970 [4]. Sporadic cases were intermittently reported from eleven endemic countries of Africa. Furthermore, several cases were reported also outside Africa, including USA outbreak in 2003 (accounting 47 cases) and few cases in UK, Singapore, and Israel in 2018-2019 and 2021 (accounting 11 cases). These cases had positive travel history to endemic countries in Africa or they had been in contact with pets infected by rodents imported from Africa. In addition, Mpox infection in these cases was not attributed to person-to-person contact.

The last cumulative data of confirmed Mpox cases from January 2022 to April 30 2024 reported to or identified by WHO from official public sources showed that 99% of all cases reported were in locations without previous history of Mpox virus exposure. The highest cumulative cases were reported from USA (32 820), Brazil (11 212), Spain (7992), Colombia (4226), France 4218), Mexico (4097), UK (3928), Germany (3841, Peru (3812), China (2357). Cumulative number of Mpox cases reported in these countries represents 81 % of all Mpox cases globally. In April 2024, a total of 528 new cases were reported which represents 21% decline over the number of new cases reported during previous month

of March 2024. In the last six months the number of reported Mpox cases fluctuated between 500 to 1000 cases (average 776 cases per month). Epidemiological evaluation of Mpox cases showed that 96.4% of cases were male of median age of 34 years (29-41 years). The most frequent transmission rout was sexual intercourse (83.6%). Only one symptom of Mpox infection was reported in 88.6% of cases. Most frequently it was rash which could be systemic or genital following with fever. About 52% of Mpox cases suffered from HIV infection. All the characteristic of Mpox infection were consistent during current Mpox outbreak. In African region more diverse transmission is thought and may also include zoonotic exposure.

Mpox isolates are classified in two genetically distinct clades. Clade1 is more transmissible and may cause more severe disease and was confirmed in Central Afrika. Currently, there is a new outbreak in the Democratic Republic of Congo and a novel variant of Clade1 was confirmed. There is no evidence of the novel variant transmission outside of endemic countries of the Central Afrika. Clade 2 of Mpox virus is responsible for Mpox cases in the West Africa [5,6].

The rout of entry for Mpox infection may be nasopharynx, intradermal, or oropharynx. The incubation period is 6-14 days, but it can be extended up to 21 days. During incubation period the infected person is not contagious. Prodromes starts with fever, malaise, headache, sore throat, or cough. Lymphadenopathy is prominent and characteristic for Mpox infection and can be present in 90% of cases. During prodrome period infected person is contagious. The rash starts on the face and spreads centrifugally and can be seen 1-3 days after the fever. Skin lesions have typical appearance and develop through macules, papules, vesicles, pustules, and crusts. All lesions develop simultaneously at any part of the body. Person is contagious until after all the crusts have fallen off. Duration of infection is mostly 2-4 weeks. The Mpox cases during the current outbreak 2022 presented clinical diversity from those of previously reported. The main route of transmission was sexual intercourse. In these cases, the incubation period is shorten due to direct virus injection. The skin rash can be the primary symptom at the onset of disease and my appear before the fever and other systemic symptoms. In some cases, prodromal symptoms are absent. Moreover, the lesions are asynchromatous in different stages of development and in some cases skin lesions skip morphological phases, e. g. papule progression to the ulcer. In one large-scale study less than 20 total lesions were recorded in 82% of Mpox cases, isolated single lesion in 20%, and less than 5 total lesions in 72% of Mpox cases. Lymphadenopathy was described in 52% of Mpox cases. Very rare the morbilliform rash was also recorded. Diverse is also localization of skin lesion. Predominantly anogenital and perioral lesions were involved. Isolated lesions in genitalia or perineal or perianal area can be seen without skin involvement in other sites. Male cases may have many genital lesions afflicting penis, scrotum, or pubis. The lesions may be associated with edema around genital sores or with enlargement of penile glans or foreskin. The Mpox lesions can also involve perineal area, buttocks, anal margin, and rectum mucosa. Proctitis can the complications of Mpox infection in these cases. Other frequently affected region is perioral. Involved oral mucosa can be associated with ulcers. The tongue lesions are round, white, and concave in shape. If tonsils are involved, the lesions may induce difficulty in swallowing due to edema. Serious complications were recorded including bacterial infections developing in abscesses. Large ulcerations or plaques can be developed when the lesions coalesce. Novel severe consequences reported in 2022 Mpox outbreak were myocarditis, epiglottitis, Quincy peritonsillar abscess, bowel perforation with accompanying abscesses in cases with rectal involvement. Cytokine storm resembling cytokine storm in Covid infection was also recorded [7-12].

Mpox infection is a self-limiting disease. In the 2022 Mpox outbreak, majority of cases was treated symptomatically. Antiviral treatment should be considered in cases with severe infection or at risk of severe infections. The risk group of severe Mpox infection includes immunocompromised patients, children younger than 8 years of age, pregnant women, and person with severe skin disease or severe Local Mpox infection. In risk group of cases, vaccinia immune globulin intravenous (VIGIV) can be used for prophylactic purpose in an exposed person to Mpox infection and in pregnant women with severe Mpox disease [13,14]. Currently, no specific therapy against Mpox infection exists. However, three antiviral drugs approved for treatment of smallpox can be used to treat Mpox infection. Tecovirimat is approved by the regulatory authorities for treatment of smallpox. It is recommended as the first line therapy of Mpox infection. Bridocidofovir is approved for smallpox and recommended as the secondary line therapy of Mpox infection [15]. Cidofovir is the third line therapy of Mpox infection and approved for cytomegalovirus retinitis in AIDV patients. Nowadays, twenty-three new molecules and monoclonal antibodies underwent medical research.

The data from Mpox outbreak 2022 suggested that unvaccinated individuals have 14- times higher risk of Mpox disease compared to individuals who were vaccinated. Previous smallpox vaccination was found to provide 85% protection against Mpox infection. Currently, WHO recommended the ring vaccination strategy which comprises the risk populations and their close contacts. Mpox vaccination can be used as a pre-exposure prophylaxis in individuals in risk of exposure. Communities at high risk of Mpox exposure or high-risk behaviors are men who have sex with men (MSM), occupational sex workers, LGBTQ individuals. In risk group also belong health workers administering smallpox vaccines, laboratory personnel working with orthopoxvirus or performing diagnostic tests. In addition, vaccination is also recommended to physicians, scientists and health providers who could be in contact with infected person or infected material, or Mpox virus as a subject of research or others. In endemic countries, vaccination is recommended to individuals who were in face-to-face exposure to Mpox infection or in direct physical contact including sexual intercourse or in contact with contaminated materials such as clothing or bedlinen. Post-exposure prophylaxis is recommended to individuals who have had contact with a confirmed Mpox case. Such group of individuals comprises of immunosuppressed patients and risk group individuals. Vaccina can be administered within 4 days of the first exposure to infection and may prevent onset of Mpox disease. Administration between 4-14 days may decrease symptoms, although may still be effective in decreasing symptoms, although may not prevent the disease. Nowadays, two vaccines are recommended in vaccination program for Mpox infection. The first one is Jynneos (Imavex) which comprises an attenuated non-replicated virus. Two doses are recommended to use in 28-day gap between doses. This vaccine can be used in pre-exposure and post-exposure purposes. ACAM2000 (Imvamune) is a live attenuated vaccine and is contraindicated to immunocompromised individuals including HIV patients or pregnant women [16-18]. Recent WHO data demonstrate a global trend toward a decrease in the number of new Mpox cases globally. There could be several reasons while Mpox infection have recently decreased worldwide. One of the reasons could be increasing immunity in

the most affected population group due to natural immunity and vaccination, behavioral changes, and significant decrease in the number of cultural and social activities by the risk groups. One online survey documented that 48% of MSM reduced their sex-partners, 50% of them reduced one-time sexual intercourse and 50% of them reduced sex with partners met on dating apps or at sexual venues [19].

The last epidemiological update recorded by WHO in May 31. 2024 documented a low level of transmission of Mpox infection globally. While the current outbreak trends downward, transmission continues in some endemic countries in Africa with rising trend in the last months having a global health concern. However, the long -term risk assessment for Mpox infection is moderate for the general population in countries with historical Mpox transmission and their neighbors. The long -term risk is moderate also for MSM, trans and gender diverse people, and occupational sex workers. Moreover, the long- term risk is low for general population in countries not affected prior to the current Mpox outbreak. However, the long -term risk is high for the general population in the Democratic Republic of Congo.

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