

robust enough from approximately the 6th year of life (Fig. 1) (Tian X, et al. *Virologica Sinica* 2021; 36: 373-81). Furthermore, the development of immunity against one HAdV species appears to provide some cross-immunity against others. Loss of T-cell responses against HAdVs is associated with more severe infections, particularly in children. In these cases, the most frequent HAdV species is C, which is usually associated with hepatitis (Lion T. *Clin Microb Rev* 2014; 27: 441-62).

In light of these data, the HAdV hypothesis for unexplained childhood hepatitis gains strength. The period of social isolation of more than 2 years caused by the COVID-19 pandemic has reduced natural exposure to HAdVs. In children between 1 and 7 years of age, in whom immunity against HAdVs has to be strengthened by repeated infections, the level of protection would nowadays be deficient. As social life returns to normal, new HAdV infections would be more severe in a subset of unexposed young children between 2 and 6 years old. For those older than 7 years old, the immunity acquired before the COVID-19 pandemic still would be robust enough to protect against severe HAdV disease (Fig. 2). The recognition of HAdV type 41F, usually causing gastrointestinal disease, as the most likely responsible for these cases of hepatitis supports this hypothesis.

More definitive data are needed before accepting the adenovirus hypothesis for the current unexplained childhood hepatitis. The causal relationship has not yet been reliably confirmed, and whether other specific HAdV variants or types may be particularly responsible. It is important to clarify these aspects, since confirmation might support the threat of rebounds for other illnesses (allergies, infections, etc.) following lifting restrictions and prolonged social isolation.

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International outbreak of monkeypox in men having sex with men

On May 17, seven patients with monkeypox were reported in the United Kingdom (Mahase E. *BMJ* 2022). Since that time, more than 2500 cases have been reported in 30 non-African countries, including Spain, Portugal, Italy, Sweden, USA, Canada, and Australia by the end of June 2022. Almost all are gay men under

the age of 40. In Spain, the Ministry of Health has already confirmed 120 cases and there are another 50 suspects. Almost all have been diagnosed in Madrid.

Monkeypox virus (MPXV)

It is a double stranded DNA virus that belongs to the orthopoxvirus family. Rodents (rats, squirrels, etc.) are its main reservoir. Monkeys – like humans – become infected from these animals, so it is a zoonosis. The virus was first isolated in 1958 in monkeys that fell ill at a research facility in Denmark (Cho C & Wenner H. *Bacteriol Rev* 1973).

The first human case of MPXV infection was described in 1970 in a child from the Democratic Republic of the Congo, formerly Zaire (Ladnyj I, et al. *Bull WHO* 1972). MPXV is similar to the virus that caused smallpox, the only infectious disease that has been eradicated from the world to date. The WHO considered it extinct by 1980.

People vaccinated against smallpox depicts some protection against monkeypox. Therefore, almost all current cases have been described in young people, all of whom being unvaccinated against smallpox.

Transmission

Monkeypox is a rare viral infection in humans. A hundred cases are reported each year in West African countries, such as Nigeria, Cameroon, the Central African Republic, and the Republic of the Congo. In Nigeria alone, 241 cases have been confirmed since 2017, eight of which have died (Nguyen P et al. *Emerg Infect Dis* 2021). So far in 2022, 15 more cases have been diagnosed in Nigeria. Outside of West Africa, reported cases are almost always related to travel to endemic areas.

Transmission usually occurs when humans come into close contact with infected animals or contaminated meat. Small skin wounds or mucosal exposure facilitate contagion. In 2003, there was an outbreak in the U.S. with 47 affected. The source of the contagion was squirrels sold as pets from a farm near Chicago, where they had grown up alongside rodents imported from Ghana, which turned out to be infected with MPXV (Reed K, et al. *N Engl J Med* 2004).

Clinical manifestations

The disease usually self-limits in less than a month, with the appearance of fever, headache, arthromyalgias, neck adenopathies, and characteristic

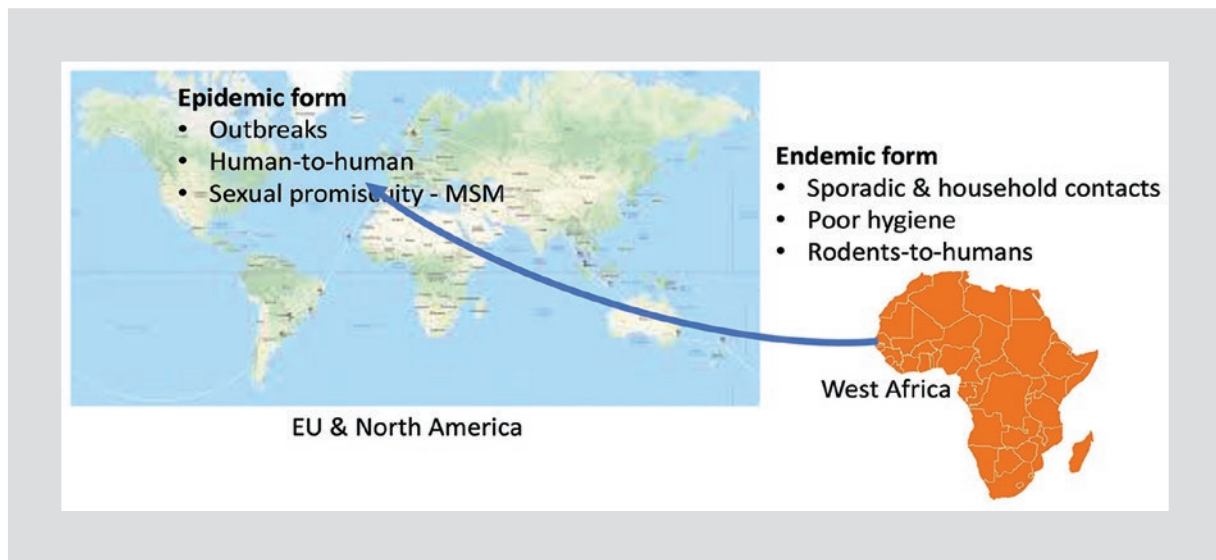


Figure 1. Monkeypox transmission & Clinical forms.

skin lesions, which can range from a few to hundreds. The differential diagnosis is with chickenpox, although smallpox lesions begin on the face, last longer, and depict central umbilication and purulent material, being able to leave a scar when the scabs fall. Serious complications can occur in 5-10% of cases (pneumonia, encephalitis, etc.) and even be fatal.

Sporadic endemic cases and epidemic outbreaks

Until now the endemic form was the most frequent clinical presentation, being low the contagiousness, predominantly from infected rodents and in situations of poor hygiene with exposure to contaminated clothes or sheets, in addition to direct contact with infected animals.

Outbreaks have rarely been reported to date. The best known is the one that occurred in the United States in 2003 with squirrels sold as pets. The current outbreak among men having sex with men corresponds to an epidemic form of the disease. What is new is the high contagiousness by sexual means, hitherto unrecognized (Fig. 1).

Characteristically, skin lesions especially affect the genitals, the perianal region, and the oral cavity. Many of the current cases have been diagnosed along with other sexually transmitted infections. All cases identified in the current outbreak in Europe and North America are progressing favorably. They have been isolated and their contacts have been studied to try to

find out the origin of the infection and stop possible new cases.

The health authorities have focused their attention on gay men, so that the diagnosis is considered before any rash that recalls chickenpox or secondary syphilis. Many of those infected belong to chains of transmission of people who have frequented saunas popular among the gay community or who have participated in parties where drug use was consumed ("chemsex").

Origin of the current outbreak

Material from a skin lesion collected from a Portuguese patient has shown that viral sequences cluster phylogenetically with the West African clade and are closely related to MPXV associated with cases exported from Nigeria to the United Kingdom, Israel, and Singapore in 2018-2019 (Yinka-Ogunleye A, et al. *Lancet Infect Dis* 2019; Mauldin M, et al. *J Infect Dis* 2022). The virus could have been circulating outside of the countries where it is endemic, but had not led to major outbreaks as a result of COVID-19 lockdowns, social distancing, and travel restrictions. Coming back to "normality" could have contributed to the current outbreak, this time fueled by sexual transmission.

Prevention and treatment

The number of human cases of monkeypox is expected to increase rapidly and in different countries. The WHO has organized an emergency meeting next

week in Geneva to discuss the control measures that will need to be taken to contain the epidemic. There are two oral antivirals to treat human infection with MPXV, tecovirimat, and brincidofovir (*Russo A, et al. Expert Rev Anti Infect Ther 2021*). Tecovirimat seems to be the most active (Adler H *et al. Lancet Infect Dis* 2022).

On the other hand, the smallpox vaccine is effective in preventing the spread of the MPXV. In addition, there is a formulation of the vaccine that

specifically protects against the two viruses. Health authorities are evaluating the administration of these smallpox vaccines to risk groups to contain the current outbreak, a strategy known as “ring vaccination.”

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