

Monkeypox Virus – New Challenges of Modernity: Experimental Organizational and Legal, Clinical and Pharmacological Studies

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Abstract. The article presents the results of the research for the new challenges of today regarding the incidence of monkeypox virus using organizational and legal, clinical and pharmacological approaches to analyze epidemiology, risks, symptoms, vaccination opportunities, recommendations for detection, pharmacotherapy and prevention. Complex experimental organizational and legal, clinical and pharmacological study was conducted. The research was conducted on the basis of the disciplines of healthcare organization, pharmacy organization and management, forensic pharmacy, clinical pharmacy, management for different groups of patients

and was based on the principles of evidence-based medicine, evidence-based pharmacy. Issues of epidemiology, risks, symptoms, vaccination of monkeypox disease were studied. Recommendations of the WHO and scientific circles concerning the effectiveness of detection, pharmacotherapy, and prevention of monkeypox were analyzed.

Keywords: monkeypox virus, organizational and legal, clinical and pharmacological studies, evidence-based medicine, evidence-based pharmacy, epidemiology, risks, monkeypox symptoms, monkeypox vaccination, monkeypox recommendations.

Introduction. Ensuring the right of citizens and patients [1, 2] to access to essential medicines is a fundamental achievement, which is based on the principles of medical and pharmaceutical law, evidence-based medicine, and pharmacy [3-8]. In Ukraine, they are enshrined in the Article 3 of the Constitution of Ukraine [9] and Article 4 of the Law of Ukraine of "Basics of Ukrainian legislation concerning healthcare" [10]. The COVID-19 pandemic has shown the importance of pharmaceutical provision of the healthcare system with medicines and vaccines to increase the level of accessibility for all patient groups in the system of legal relations "doctor-patient-pharmacist" [11-23].

Timely identification of the problem (discussion, information, action plan, etc.) associated with pandemics obliges the specialists of the World Health Organization (WHO) to monitor the situation with the development of the incidence in all states, the WHO members located in five regions (America, Africa, Europe, Eastern Mediterranean, Western Pacific). Therefore, at present, the close attention of the WHO, along with the spread of COVID-19 [24, 25] and other diseases, has attracted the monkeypox virus. The name monkeypox comes from the initial discovery of the virus in monkeys in a Danish laboratory in 1958. The first human case was identified in a child in the Democratic Republic of the Congo in 1970 [26]. Today, monkeypox is a disease of global public health importance as it affects not only West and Central Africa, but the rest of the world.

The purpose of the work was to study the new challenges of today regarding the incidence of monkeypox virus using organizational and legal and clinical and pharmacological approaches for the analysis of epidemiology, risks, symptoms,

vaccination opportunities, recommendations for detection, pharmacotherapy, disease prevention.

Materials and methods. A complex experimental study was carried out: organizational and legal, clinical and pharmacological, clinical and pharmacological. Organizational and legal, clinical and pharmacological approaches included the study of the problem of monkeypox virus incidence using traditional research methods. The study was conducted at the intersection of the organization of healthcare, organization and management of pharmacy, forensic pharmacy, clinical pharmacy, management for different groups of patients and was based on the principles of evidence-based medicine, evidence-based pharmacy [27-38].

The study was conducted from April 2022 to June 2022.

The information base of the study consisted of scientific works of foreign and domestic scientists on the topic of the article (more than 300). The review of scientific sources of literature was carried out taking into account the recommendations of the Cochrane Society for PICO: P (population) – the population of patients infected with the monkeypox virus; I (intervention) – recommendations for clinical and pharmacological examination of patients infected with the monkeypox virus; C (comparison) – comparison in research technology, experimental study; O (outcomes) – research results. Based on a review of published qualitative strategy and management research, the author identifies highly innovative academic articles, that is, a study that demonstrates substantial novelty in every part of the research process. The author works through these articles in detail to demonstrate their novelty, highlighting concrete ways in which scholars have innovated three interconnected parts of the research process: data generation, data analysis, and presentation of findings.

Among the traditional research methods used are regulatory, documentary, normative and legal, retrospective, clinical and pharmacological, comparative, system, forensic and pharmaceutical and graphic.

Microsoft Excel 2010 (descriptive characteristics: minimum and maximum value, average value) was used to process the results and determine the consistency between the studied parameters.

The research of the article is a fragment of research work of the Kharkiv Medical Academy of Postgraduate Education on "Improving the organizational and legal procedure for providing patients with drugs from the standpoint of forensic pharmacy, organization and management of pharmacy" (state registration number 0116U003137, terms 2016-2020) and "Pharmaceutical and medical law: integrated approaches to the system of drug circulation from the standpoint of forensic pharmacy, organization and management of pharmacy" (state registration number 0121U000031, terms 2021-2026).

Results and discussion. In the period from 01/01/2022 to 06/15/2022, the WHO reported 2103 laboratory-confirmed cases of monkeypox virus infection (one death) from 42 states [39].

Epidemiology.

In 2003, the first outbreak of monkeypox outside of Africa occurred in the United States. The outbreak has been linked to contact with infected domestic prairie dogs. Domestic animals were kept together with Gambian pouched rats brought into

the country from Ghana. This outbreak resulted in over 70 cases of monkeypox in the US. Monkeypox has also been reported in travelers from Nigeria: to Israel in September 2018; to the United Kingdom – in September 2018, December 2019, May 2021, May 2022; in Singapore - in May 2019; to the United States of America - in July and November 2021 [26]. Portugal reported five confirmed cases of monkeypox and more than 20 suspected cases. All patients were young people. Spain also reported eight suspicious cases [41]. A case of monkeypox was also discovered for the first time in Germany [42].

As of June 15, 2022, there were 1158 confirmed cases of monkeypox virus in 22 countries of the European Union (Table 1) [40].

Table 1. Notified cases of monkeypox virus in EU countries (as of 15.06.2022).

EU country	Number of cases of monkeypox virus
Malta	1
Poland	1
Greece	2
Latvia	2
Norway	2
Romania	2
Hungary	3
Island	3
Finland	3
Austria	4
Czech Republic	6
Slovenia	7
Denmark	7
Sweden	9
Ireland	10
Belgium	36
Italy	48
Netherlands	80
France	125
Portugal	231
Germany	263

EU country	Number of cases of monkeypox virus
Spain	313
Total	1158

The EU countries with the highest number of cases were Spain (313), Germany (263), Portugal (231), France (125). Other countries: The United Kingdom (524), Canada (159), United States of America (72).

Recorded cases of monkeypox in endemic countries for the period 12/15/2021-05/01/2022 are given in Table 2 [43].

Table 2. Number of monkeypox cases in endemic countries (December 15, 2021 to May 1, 2022).

Country	Time period	Cumulative cases	Cumulative deaths
Cameroon	15 December 2021 to 22 February 2022	25	<5
Central African Republic	4 March to 10 April 2022	6	<5
Democratic Republic of the Congo	1 January to 1 May 2022	1238	57
Nigeria	1 January 2022 to 30 April 2022	46	0

Today, more than 95 percent of cases of disease in Great Britain are men. The majority of cases of monkey pox were detected in young men with a certain sexual orientation [44].

There is no significant risk of monkeypox spreading in Ukraine [45]. The chances of monkeypox spreading on the territory of Ukraine are very small [46]. Subsequently, cases of monkeypox were registered in Ukraine. The Ministry of Health of Ukraine does not expect an epidemiological outbreak of BOS and allows the possibility of its localization [47].

Countries endemic for monkeypox: Benin, Cameroon, Central African Republic, Democratic Republic of Congo, Gabon, Ghana (only found in animals), Liberia, Nigeria, Republic of Congo, and Sierra Leone [43].

Scientists also express concern about the sudden outbreak of monkeypox and its continued spread, especially in non-endemic countries. In May 2022, several cases of monkeypox were detected in several non-endemic countries (Table 3) [48].

Risks. The scale of the outbreak and spread of monkeypox pose real risks to society. The longer the monkeypox virus circulates, the more widely it will expand its scope, and the stronger the spread of the disease will be in non-endemic countries. Monkeypox endemic is usually geographically limited to West and Central Africa. The identification of confirmed and suspected cases of monkeypox without any travel to endemic areas is atypical in many countries [49, 50].

Table 3. Number of cases of monkeypox virus in non-endemic countries (as of May 21, 2022).

Country	Confirmed	Suspected
Australia	1-5	-
Belgium	1-5	1-5
Canada	1-5	11-20
France	1-5	1-5
Germany	1-5	-
Italy	1-5	-
Netherlands	1-5	-
Portugal	21-30	-
Spain	21-30	6-10
Sweden	1-5	-
United Kingdom	21-30	-
United States of America	1-5	-
Total	92	28

Various animal species have been found to be susceptible to the monkeypox virus. This includes rope squirrels, tree squirrels, Gambian pouched rats, dormice, non-human primates, and other species. Further research is needed to determine the exact reservoir and circulation of variola virus in nature [26].

Monkeypox is caused by a virus of the same name, closely related to smallpox, which has now been eradicated from the planet. Both viruses are members of the Orthopoxvirus genus of the Poxviridae family. Monkeypox was first identified in 1958 when outbreaks of the disease that causes smallpox were found in monkeys held in captivity for research. The virus is currently endemic in Central and West Africa [51].

Informing the population of all countries is important and necessary. Cross-protective immunity from smallpox vaccination would be limited to the elderly. Historically, smallpox vaccination has been shown to protect against monkeypox. Populations around the world under the age of 40 or 50 no longer benefit from the protection provided by previous smallpox vaccination programs and are at risk. Young people living in non-endemic countries have little immunity to monkeypox because the virus does not exist there [43].

The individual risk of infection through contact with a person with monkeypox depends on the nature and duration of contact. The likelihood of transmission between people without close contact is considered low. Mortality is higher among children and persons under 35 years of age. Immunocompromised individuals are particularly at risk of severe illness. Family members are at moderate risk of infection; close contacts (for example, immediate neighbors on an airplane); caregivers (for example, healthcare workers who did not take preventive measures). In society, the risk of transmission is considered negligible. Transmission between individuals mainly occurs by airborne droplets. Monkeypox virus is transmitted from one person to another through close

contact with lesions, bodily fluids, airborne droplets, and contaminated materials such as bedding [26].

Risks of infection exist in the event of a rash, fever, discomfort, or malaise. You need to see your doctor and get tested for monkeypox. If monkeypox is suspected or confirmed, the patient should be isolated until the scabs fall off and abstain from sex. During this period, patients may receive supportive care to relieve the symptoms of monkeypox. Monkeypox care should include appropriate personal protective measures (masks, cleaning of objects and surfaces) [43]. Belgium was the first to oblige those infected with monkeypox to observe quarantine [52].

During outbreaks of monkeypox, close physical contact with infected humans is the most significant risk factor for infection with monkeypox virus. Laboratory confirmation of suspected cases is important. Suspicion of the presence of a similar disease in the patient community or among contacts should be further investigated [43].

Symptoms. Monkeypox is a viral zoonotic disease that occurs mainly in the rainforest regions of central and western Africa and occasionally spreads to other regions. Monkeypox usually lasts 2 to 4 weeks. Severe cases are possible. Recently, the case fatality rate has been around 3–6%. Monkeypox is transmitted to humans through close contact with an infected person or animal, or with material contaminated with the virus. Monkeypox virus is transmitted from one person to another through close contact with lesions, bodily fluids, airborne droplets, and contaminated materials such as bedding [26, 43, 52].

Symptoms include fever (above 38.5°C), headache, muscle pain, back pain, swollen lymph nodes, chills, asthenia (weakness). A rash usually appears. The rash often starts on the face and then spreads to other parts of the body, including the genitals. The rash goes through different stages and may look like chicken pox or syphilis before finally forming a scab that later falls off. The incubation period is usually 6 to 16 days, but can be up to 21 days. When the crust falls off, the person ceases to be contagious [41, 42].

Severe cases are more common among children and are related to the degree of exposure to the virus, the health of the patient, and the nature of the complications. Complications of monkeypox can include secondary infections, bronchopneumonia, sepsis, encephalitis, and corneal infection with consequent loss of vision. The case fatality rate for monkeypox ranged from 0 to 11% in the general population and was higher among young children. Recently, the lethality rate has been about 3–6% [26].

Symptoms usually appear between 5 and 13 days after infection, although they may take up to 21 days to appear. Against the background of acute fever, a rash appears that concentrates on the face, arms, and legs, and then spreads to other parts of the body (oral cavity, genitals, and cornea). The rash progresses to the formation of scabs, which subsequently fall off, in some cases large areas of skin may fall off the body. Symptoms often subside within a month, but one in ten cases can be fatal. Considering that the rash is observed in many other diseases, such as chicken pox and measles, WHO recommends PCR tests for diagnosis [51].

Vaccination.

WHO suggests that national health authorities conduct vaccination against monkeypox [53]. The monkeypox vaccine was the key to eradicating smallpox decades

ago (85% effective). However, the original first-generation smallpox vaccines are no longer available to the general population of the world. A newer vaccine based on the smallpox vaccine was approved for the prevention of monkeypox in 2019. However, it has not yet become widespread in medical practice [51].

ACAM200 (Imvamune) and JYNNEOS™ (Imvanex) are the two vaccines currently licensed in the US to prevent monkeypox virus infection (Table 4).

Table 4. Monkeypox vaccines.

No.	Naming	Status	Country
1.	ACAM200 (Imvamune)	licensed smallpox vaccine	USA
2.	JYNNEOS™ (Imvanex)	licensed smallpox vaccine	USA

When vaccinating against monkeypox, the effectiveness of the vaccine, the method of obtaining the vaccine after contact with the monkeypox virus, the possibility of revaccination after infection, and the possible risks of vaccination against monkeypox are taken into account. Vaccination with ACAM2000 (Imvamune) is recommended for certain Orthopoxvirus technicians and military personnel. JYNNEOS (Imvanex) vaccination is recommended as an alternative to ACAM2000 for certain individuals at risk of orthopoxvirus infection [55].

Early vaccination reduces the risk of contracting monkeypox. It is recommended to administer the vaccine within 4 days of infection to prevent the onset of the disease. Vaccination given 4 to 14 days after the date of exposure may reduce the symptoms of the disease, but not prevent it. The ACAM2000 vaccine (Imvamune) may cause more side effects and adverse events than the newer JYNNEOS vaccine (Imvanex) [55].

Recommendations for detection, pharmacotherapy, prevention.

Governments, health partners and civil society must act urgently and jointly control the detection of monkeypox [49, 56]:

- ✓ carry out enhanced surveillance, contact tracing and infection prevention and control;
- ✓ intensive community involvement and clearer communication;
- ✓ genuine and selfless regional cooperation – urgently now and in the long term.

In non-endemic countries where monkeypox cases have been identified, further public health investigations are ongoing, including extensive case finding and contact tracing, laboratory testing, clinical management, and isolation with supportive care [57].

The WHO convenes experts to discuss vaccination recommendations. Physicians should be prepared to administer pharmacotherapy for atypical rashes (spots, papules, vesicles, pustules, scabs). Raising awareness among potentially affected communities, as well as healthcare and laboratory workers, is essential to detect and prevent further secondary cases and effectively manage the current outbreak [43].

Contact tracing is a key public health measure to control the spread of infectious agents, in particular monkeypox virus. Healthcare workers caring for patients with

suspected or confirmed monkeypox should follow standard precautions as well as contact and airborne precautions. Standard precautions include strict hand hygiene, proper handling of contaminated medical equipment, laundry, waste, cleaning, and disinfection of surrounding surfaces. Immediate isolation of suspected or confirmed cases in a separate room with adequate ventilation, private bathroom and staff is recommended. Recommended personal protective equipment includes gloves, gown, medical mask, and eye protection (goggles or face shield). The patient should also be instructed to wear a medical mask when in close contact (less than 1 m) with healthcare workers or other carriers of monkeypox virus. A bandage, sheet, or gown may be used to cover the affected areas to minimize potential contact with the lesions. Precautions based on isolation and transmission should be continued until the symptoms disappear (including the disappearance of any rash and crusts that have fallen off and healed) [51].

Pharmacotherapy for monkeypox includes the specific antiviral drug TPOXX (INN Tecovirimat). The antiviral drug TPOXX (INN Tecovirimat) has been approved by the European Medicines Agency, Health Canada and the US Food and Drug Administration for the treatment of smallpox. TPOXX (INN Tecovirimat) is included in research or humanitarian protocols, especially in patients with severe symptoms or who are immunosuppressed. If smallpox vaccines are available in the country, vaccination of high-risk close contacts should be considered after assessing the risks and benefits. In severe cases, use the option of treatment with the registered antiviral drug TPOXX (INN Tecovirimat) if it is available in the country [41].

A fact sheet for medical professionals on the pharmacotherapy of monkeypox has been developed. The clinical management of monkeypox must be fully optimized to relieve symptoms, manage complications, and prevent long-term consequences. Patients should be offered fluids and food to maintain an adequate nutritional status. Secondary bacterial infections should be treated as indicated [26, 41].

The WHO supports Member States in surveillance, preparedness and response to monkeypox outbreaks in affected countries. The European Commission's Health Preparedness and Response Authority has contracted Bavarian Nordic to procure 109,090 doses of their 3rd generation vaccine JYNNEOSTM (Imvanex) in response to the current outbreaks of monkeypox. As the number of cases continues to rise, this agreement will make vaccines quickly available to all EU member states, Norway and Iceland. Some Member States have already granted national exemptions allowing temporary use of monkeypox virus vaccine. The European Medicines Agency stands ready to support Member States in facilitating such exemptions and has actively contacted the company to expedite the regulatory process. In its risk assessment, the European Center for Disease Control and Prevention (ECDC) recommended that affected countries consider early post-exposure vaccination to prevent or lessen the severity of the disease [57].

The WHO's goal is to help countries contain monkeypox virus infection and stop the outbreak with proven control measures. The WHO does not recommend mass vaccination against monkeypox. Smallpox vaccines are thought to provide some degree of protection against monkeypox, but there are insufficient clinical data and vaccine availability is limited [58, 59].

The World Health Network (WHN) is declaring the monkeypox outbreak a public health emergency. Today, the monkeypox pandemic is of global concern because it is not limited to one country or region and must be eliminated through immediate action wherever there is community transmission of the virus. to ensure minimal effort and minimal impact of this outbreak [60, 61].

Recommendations include the need for availability of testing without travel restrictions, known contact with infected individuals, belonging to certain communities

Information is needed on the importance of isolation from others whose symptoms may indicate infection, even before a diagnosis of monkeypox is confirmed. Information is needed about the possibility of infection outside the gay community, in which most transmission occurred during the initial spread of monkeypox around the world, to avoid any misunderstanding or perceived stigma that would lead people not to report their symptoms and not get tested.

Provision of premises in which isolation and quarantine are possible with the necessary medical support. Providing financial and other support to individuals who need to be isolated or quarantined [61].

Among the recommendations is the importance of timely development of plans for the targeted use of vaccination to contain the outbreak of monkeypox. Delayed action leads not only to greater harm and suffering for those infected, but also to a much greater social impact of the interventions needed to contain further consequences. Conditions today are such that stopping the outbreak is possible with widespread case-finding and contact tracing. Bilateral communication about the risks associated with monkeypox, involving affected communities in prevention, detection and treatment are important to prevent the further spread of monkeypox [61, 62].

It should be noted that there are atypical aspects of monkeypox outbreaks that are of serious scientific, public, and social concern. The number of cases of monkeypox detected in the outbreak 2 weeks after the first case was detected exceeded the total number of cases previously detected in a single country. The scientific, environmental, and social causes of this phenomenal increase remain a mystery and need to be urgently determined with a single universal approach. Ongoing epidemiological studies have not linked the affected individuals to travel to monkeypox-endemic areas of Africa. This may indicate that the monkeypox virus may have been spreading undetected in Europe for some time. There is no answer to the question whether these events are associated with a change in the transmission properties of the monkeypox virus or increased virulence. Compared to RNA viruses, monkeypox virus is a large DNA virus that makes itself more stable and efficient than RNA viruses at detecting and eliminating mutations. The problem of sexual transmission of monkeypox virus requires further study. Monkeypox outbreaks expose serious gaps in understanding the dynamics of virus transmission and the ever-changing epidemiological characteristics of the disease. The emergence and rapid spread of monkeypox in Europe has generated intense scientific, political and media activity [63, 64].

The results of the experimental organizational and legal, clinical and pharmacological studies indicate the need to continue the study of all aspects of infection, distribution, diagnosis, pharmacotherapy and prevention against monkeypox virus.

Conclusions. A comprehensive experimental organizational and legal, clinical and pharmacological study was carried out. It was indicated that the study includes different disciplines (organization of healthcare, organization and management of pharmacy, forensic pharmacy, clinical pharmacy, management for different groups of patients, which was based on the principles of evidence-based medicine, evidence-based pharmacy. The issues of epidemiology, risks, symptoms, vaccination of monkeypox disease. The countries with the largest number of detected cases of monkeypox are given. The need to inform the population of all countries about the risks of infection with the monkeypox virus was justified. The vaccines against smallpox of monkeys features of vaccination were given. The recommendations of the WHO and the scientific community concerning the effectiveness of detection, pharmacotherapy, and prevention of monkeypox were analyzed.

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