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MPOX: FROM EPIDEMIOLOGICAL TRENDS TO MODERN IMMUNOPROPHYLAXIS STRATEGIES. LITERATURE REVIEW

Ayan M. Tuyakov[1]*, Gulzhan A. Zhapparova[1], Talshyn M. Tlenchieva[1], Balzhan Sh. Myrzakhmetova[1], Kuandyk D. Zhugunisov[1], Lespek B. Kutumbetov[1], Zhazira Ye. Omarbekova[2], Dariya M. Shabdarbayeva[2], https://orcid.org/0000–0001–9463–1935

[1] "Limited Liability Partnership 'Research Institute for Biological Safety Problems', Zhambyl Region, Korday District, urban-type settlement of Gvardeyskiy, Republic of Kazakhstan;
[2] NCJSC "Semey Medical University", Semey, Republic of Kazakhstan.

Abstract

Introduction. Mpox (the disease caused by the MPXV virus) gained global significance during the 2022–2025 outbreak; as of the analysis period, 97,281 laboratory-confirmed cases had been reported in 118 countries, and the WHO declared the situation a Public Health Emergency of International Concern (PHEIC) on 14 August 2024. The expanded geographic circulation and the presence of vulnerable groups necessitate reassessment of control measures and vaccination strategies.

Objective. To analyse current features of Mpox spread and to evaluate the effectiveness of available preventive vaccine measures in the context of importation risk.

Search strategy. A critical review of peer-reviewed literature and official reports published between 2010 and 2025 was conducted; included sources comprised scientific publications, regulatory documents and surveillance data. Analysis was structured around mpox epidemiology and spread, risk groups and clinical features, and vaccine platforms (licensed products and candidates), with data classified as preclinical or clinical.

Results. Clinical presentation ranges from typical staged cutaneous eruptions to atypical anogenital forms; disease is more severe in people living with HIV. No confirmed cases were reported in Kazakhstan (July 2025). Regarding vaccines: the non-replicating MVA-BN shows a favourable profile (two doses - seroconversion ≈89%; estimated effectiveness ≈82%, 95% CI 72-92%; one dose ≈76%, 95% CI 64-88%); ACAM2000 is highly immunogenic (seroconversion ≈94-97%) but limited by safety concerns; LC16-KMB is an alternative in specific scenarios. Emerging candidates (attenuated dBTF, mRNA BNT166, VLP constructs) demonstrate promising preclinical / early clinical results, but data are limited by small sample sizes and lack of direct comparative studies.

Conclusions. Priorities include ensuring access to non-replicating vaccines and targeted PrEP/PEP programmes, strengthening surveillance and laboratory readiness, standardizing correlates of protection, and conducting head-to-head and large non-human primate (NHP) / clinical studies to enable evidence-based ranking of vaccine platforms.

Keywords: *Monkeypox virus (MPXV); epidemiology; vaccines.*

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Резюме

МРОХ: ОТ ЭПИДЕМИОЛОГИЧЕСКИХ ТЕНДЕНЦИЙ К СОВРЕМЕННЫМ СТРАТЕГИЯМ. ОБЗОР ЛИТЕРАТУРЫ

Аян М. Туяков[1]*, Гульжан А. Жаппарова[1], Талшын М. Тленчиева[1], Балжан Ш. Мырзахметова[1], Куандык Д. Жугунисов[1], Леспек Б. Кутумбетов[1], Жазира Е. Омарбекова[2], Дария М. Шабдарбаева[2], https://orcid.org/0000–0001–9463–1935

[1] ТОО «Научно-исследовательский институт проблем биологической безопасности», Жамбылская область, Кордайский район, пгт. Гвардейский, Республика Казахстан;
[2] НАО «Медицинский Университет Семей», г. Семей, Республика Казахстан.

Введение. Мрох (болезнь, вызванная вирусом MPXV) приобрёл глобальное значение в ходе вспышки 2022-2025 гг.; по состоянию на период анализа зарегистрировано 97 281 лабораторно подтверждённый случай в 118 странах, а ВОЗ 14 августа 2024 г. объявила ситуацию PHEIC. Расширение географии циркуляции и наличие уязвимых групп требуют переоценки мер контроля и стратегий вакцинации.

Цель исследования. Проанализировать актуальные особенности распространения Mpox и оценить эффективность доступных профилактических вакцинных мер в контексте риска заноса инфекции.

Стратегия поиска. Критический обзор рецензируемой литературы и официальных отчётов за период 2010-2025 гг.; включены публикации, регуляторные документы и данные надзорных служб. Анализ проводился по направлениям: эпидемиология и распространение инфекции, группы риска и клинические особенности, вакцинные платформы (зарегистрированные препараты и кандидаты) с разделением данных на доклинические и клинические.

Результаты. Клиническая картина варьирует от типичных стадийных кожных высыпаний до атипичных аногенитальных форм; у лиц с ВИЧ течение тяжелее. В Казахстане подтверждённых случаев нет (июль 2025). По вакцинам: нереплицирующаяся MVA-BN демонстрирует благоприятный профиль (две дозы - сероконверсия ≈89%; оценочная эффективность ≈82%, 95% ДИ 72-92%; одна доза ≈76%, 95% ДИ 64-88%); ACAM2000 высокоиммуногенна (сероконверсия ≈94-97%) но ограничена рисками; LC16-KMB - альтернатива в отдельных сценариях. Новые кандидаты (аттенуированные dBTF, mRNA-BNT166, VLP) показывают многообещающие доклинические/ранние клинические результаты, но данные ограничены по размерам выборок и отсутствуют прямые сравнительные исследования.

Выводы. Приоритеты - обеспечение доступа к нереплицирующимся вакцинам и таргетных PrEP/PEP-программ, усиление эпиднадзора и лабораторной готовности, стандартизация коррелятов защиты и проведение head-to-head и крупных NHP/клинических исследований для обоснованного ранжирования платформ.

Ключевые слова: *вирус оспы обезьян (MPXV); эпидемиология; вакцины.*

Для цитирования:

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Түйіндеме

MPOX: ЭПИДЕМИОЛОГИЯЛЫҚ ҮРДІСТЕРДЕН ЗАМАНАУИ ИММУНОПРОФИЛАКТИКА СТРАТЕГИЯЛАРЫНА ДЕЙІН. ӘДЕБИЕТТІК ШОЛУ.

Аян М. Туяков[1*], Гульжан А. Жаппарова[1], Талшын М. Тленчиева[1], Балжан Ш. Мырзахметова[1], Куандык Д. Жугунисов[1], Леспек Б. Кутумбетов[1], Жазира Е. Омарбекова[2], Дария М. Шабдарбаева[2], https://orcid.org/0000–0001–9463–1935

[1] «Биологиялық қауіпсіздік проблемаларының ғылыми-зерттеу институты» жауапкершілігі шектеулі серіктестігі, Жамбыл облысы, Қордай ауданы, Гвардейский қтк, Қазақстан Республикасы;
[2] КеАҚ «Семей медицина университеті», Семей қ., Қазақстан Республикасы.

Кіріспе. Mpox (MPXV вирустың туындатқан ауруы) 2022-2025 жж. болған эпидемия барысында жаһандық маңызға ие болды, талдау кезеңіне сәйкес 118 елде 97 281 зертханалық расталған жағдай тіркелді, ал ДСҰ 2024 ж. 14 тамызда жағдайды Халықаралық маңызы бар қоғамдық денсаулық сақтау төтенше жағдайы (PHEIC) деп жариялады. Географиялық кеңеюі мен осал топтардың болуы бақылау шаралары мен вакцинация стратегияларын қайта қарауды талап етеді.

Мақсат. Mpox таралуының қазіргі ерекшеліктерін талдап, инфекцияның әкетілу қаупі контекстінде қолжетімді алдын алу вакциналық шаралардың тиімділігін бағалау.

Іздеу стратегиясы. 2010-2025 жж. жарияланған рецензияланған әдебиеттер мен ресми есептерге сыни шолу жүргізілді, талдау ғылыми жарияланымдарды, реттеуші құжаттарды және эпидемиологиялық қадағалау деректерін қамтыды. Талдау mpox эпидемиологиясы мен инфекцияның таралуы, қауіп топтары мен клиникалық ерекшеліктері, вакциналық платформалар (тіркелген препараттар және кандидаттар) бойынша, деректерді доклиникалық және клиникалық деңгейлерге бөле отырып жүргізілді.

Нәтижелер. Клиникалық көріністер типтік кезеңделген тері бөртпелерінен атиптік аногенитальды формаларға дейін өзгеріп отырады, ВИЧ-пен өмір сүретін адамдарда ауру ауырырақ өтеді. Қазақстанда расталған жағдайлар тіркелмеген (шілде 2025). Вакциналар жайлы: репликацияланбайтын MVA-BN жағымды профиль көрсетеді (екі доза - сероконверсия ≈89%; бағаланған тиімділік ≈82%, 95% сенімді интервал 72-92%; бір доза ≈76%, 95% СИ 64-88%), ACAM2000 жоғары иммуногенді (сероконверсия ≈94-97%) бірақ қауіпсіздік мәселелерімен шектелген; LC16-KMB кейбір сценарийлерде балама болып табылады. Жаңа кандидаттар (аттенуирленген dBTF, mRNA BNT166, VLP конструкциялары) доклиникалық/ерте клиникалық зерттеулерде үмітті нәтиже көрсетуде, алайда деректер үлгілерінің шағындығымен және тікелей салыстыру зерттеулерінің болмауымен шектеледі.

Қорытынды. Басты басымдықтар - репликацияланбайтын вакциналарға қолжетімділікті қамтамасыз ету және мақсатты PrEP/PEP бағдарламаларын енгізу, эпидемиялық бақылау мен зертханалық дайындықты күшейту,

қорғаныс корреляттарын стандарттау және вакциналық платформаларды дәлелді түрде рейтингтеу үшін тікелей салыстырулы (head-to-head) және ірі адам емес примат (NHP) / клиникалық зерттеулер жүргізу.

Түйінді сөздер: *маймыл шешегі вирусы (MPXV); эпидемиология; вакциналар.*

Дәйексөз үшін:

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Introduction

Monkeypox virus (MPXV) was first isolated in 1959 from cynomolgus macaques imported into Denmark; the first clinically confirmed human case was reported in 1970 in the Democratic Republic of the Congo. In 1970–1979, 47 confirmed cases were described in Central and West Africa, predominantly in children; in individual foci, secondary transmission was estimated at 3-7%, and case fatality reached ≈17%. Over time, both an expansion of the geographic range and changes in the demographic structure of cases were observed-the mean age increased from ≈4 years in the 1970s to >20 years in 2010-2019-which has been attributed to the cessation of mass smallpox vaccination, urbanization, and weakening of epidemiological surveillance [70, 9, 3, 4].

These long-term trends were highlighted by the 2022 outbreak, during which MPXV spread beyond its traditional endemic regions: cases were reported in previously non-endemic countries, and a proportion of transmission events occurred without obvious epidemiological links to travel to endemic areas, indicating cryptic circulation. According to WHO data, by 8 May 2023, 87,377 laboratory-confirmed cases and 140 deaths had been reported; the subsequent decline in the number of new diagnoses in February-April 2023 reflected the effect of response measures but did not eliminate the risk of further spread. Chronic resource shortages and weak surveillance in endemic regions facilitate the establishment of the virus in the ecological niche vacated after smallpox eradication, while the emergence of new genetic variants (including Clade IIb / B.1 lineages) calls for continuous monitoring and reevaluation of prevention strategies [3, 4, 24, 22].

Taxonomically, MPXV belongs to the genus Orthopoxvirus (family Poxviridae) and is divided into three clades: Clade I (Central African), Clade IIa (West African), and Clade IIb; the B.1 lineage predominated in the 2022 outbreak and was characterized by an increased substitution rate compared with preceding strains. The MPXV genome is a linear double-stranded DNA (~196–211 kb, ≈190 ORFs) with a conserved central region and variable terminal repeats; virions have a brick-shaped morphology (~200–250 nm) and exist in several biological forms (IMV, IEV/EEV), with IMV being the most stable in the external environment and playing a key role in inter-host transmission. Understanding genomic variability and the biological properties of these forms is important for interpreting changes in pathogenicity and transmission [31, 89, 38, 35, 15].

The clinical presentation of MPXV is broadly typical of poxvirus infections: fever, headache, myalgia, and a characteristic rash that progresses through the stages macules → papules → vesicles → pustules → crusts; the incubation period averages 10–16 days, and in most patients the rash appears within the first few days after fever onset. During the 2022 outbreak, atypical presentations were also documented (limited anogenital lesions or complete absence of rash), which complicated diagnosis and contributed to delayed detection. Severe complications include bronchopneumonia, encephalitis, sepsis, and secondary bacterial infections; in immunocompromised individuals (including people living with HIV), the disease course is generally more severe. Case fatality varies by clade (Clade I-up to ≈10%, Clade II-substantially lower) [16, 47, 33, 29].

This review summarizes historical and contemporary aspects of the epidemiology of monkeypox virus (MPXV) from its isolation in 1959 up to the global outbreak of 2022. Particular attention is paid to the evolution of vaccine platforms-from classical first-generation replicating vaccines to modern attenuated, non-replicating, and innovative constructs based on mRNA and virus-like particles. Comparison of the immunological characteristics and safety profiles of different platforms will make it possible to assess their potential for practical use and to develop recommendations within the framework of a national strategy for the prevention of and preparedness for orthopoxvirus infections.

Search strategy. The present study is a literature review addressing issues of the epidemiology, clinical manifestations, and prevention of MPOX. The search for publications was carried out in the international databases PubMed, Scopus, Web of Science, Elsevier ScienceDirect, Google Scholar, as well as in peer-reviewed journals. The review included original articles, reviews, and official communications of international organizations (WHO, CDC, ECDC), published predominantly in 2010-2025. Priority was given to full-text sources; abstracts of reports, newspaper publications, unpublished observations, non–peer-reviewed materials, and articles not relevant to the topic of the study were excluded. The sources were analyzed in the following main areas: epidemiology and spread of infection, routes of transmission, pathogenesis, clinical presentation, and prevention. As the study is based on an analysis of published data, separate ethical approval was not required.

Epidemiology and spread of MPOX

The monkeypox outbreak recorded in the Democratic Republic of the Congo (formerly Zaire) in 1980-1985 comprised 282 confirmed cases. The vast majority of patients (about 90%) were children younger than 15 years, with a mean age of 4.4 years. Case fatality among unvaccinated individuals was about 11%, and in children younger than 15 years up to 15%. No deaths were recorded

among individuals who had previously received smallpox vaccination [33, 32].

From February 1996 to October 1997, 511 suspected monkeypox cases were reported in the Katako-Kombe and Lodja areas (Kasai Oriental, Democratic Republic of the Congo), 419 of them in October 1997 alone [13]. Most patients (85%) were children aged up to 16 years. The disease was characterized by a severe course with high fever, diarrhea, generalized rash (often >100 lesions), lymphadenopathy, and impairment of ability to work for more than three days. Despite the pronounced symptomatology, case fatality remained relatively low-1.5% [74]. It was established that 22% of cases were of zoonotic origin, whereas 78% resulted from human-to-human transmission, predominantly within households and neighborhoods [45]. The scale of this outbreak, the largest until 2022, was probably related to increasing population susceptibility following the cessation of smallpox vaccination [29].

In 2003, from 15 May to 20 June, the first monkeypox outbreak outside Africa was recorded in the United States [54, 40]. A total of 72 confirmed and probable cases (37 of them laboratory confirmed) were identified in humans in six Midwestern states. The median age of patients was 28 years (range 1–55 years), and no deaths were reported. All patients had contact with infected prairie dogs (Cynomys spp.) [54]. The investigation showed that the likely source of MPXV introduction into the USA was an international shipment consisting of about 800 small mammals from Ghana to Texas. The shipment contained about 800 small mammals of nine different species, including six genera of African rodents. In response to the outbreak, importation and sale of African rodents and prairie dogs were temporarily suspended, and extensive epidemiological and virological investigations were carried out [11]. Genetic analysis revealed that the virus belonged to the West African clade [40].

From 22 September 2017 to 16 September 2018, Nigeria experienced the largest recorded MPOX outbreak in the country, 39 years after the last reported case [92, 56]. A total of 122 confirmed and probable cases were registered in 17 states, including the capital, and 7 (6%) deaths. The median age was 29 years, and 84 (69%) were men [91, 58]. The causative agent was a West African clade MPXV, with transmission occurring via both zoonotic routes and human-to-human transmission chains [91, 59]. In response, measures were implemented within the One Health framework: laboratory diagnostics and intersectoral collaboration between public health and veterinary services, and an electronic outbreak response and analysis system was introduced to improve digitalization and the timeliness of surveillance [56, 46]. Three MPOX cases detected in 2018–2019 in the United Kingdom and Israel were found to be associated with importation of infection by travelers from Nigeria [91, 68].

The global MPOX outbreak in 2022–2023 was the first of such magnitude outside endemic regions, affecting 111 countries and leading to tens of thousands of confirmed infections. The first confirmed MPOX case in the 2022 outbreak was identified in the United Kingdom on 7 May in a patient who had recently returned from Nigeria [67]. As of 8 August 2022, 2,914 confirmed and 103 probable monkeypox cases had been reported in the United Kingdom-a total of 3,017 [67]. On 21 May 2022, WHO issued an emergency communication regarding the onset of a multi-country MPOX outbreak in non-endemic countries. At that time, 92 confirmed and 28 suspected cases had been reported in 12 countries, including Australia, Belgium, Canada, France, Germany, Italy, the Netherlands, Portugal, Spain, Sweden, the United Kingdom, and the United States [81]. There are suggestions that MPOX virus may have been circulating unnoticed in European countries long before its official identification in May 2022, which indicates the possibility of underestimated or unrecognized transmission in the early stages of the outbreak [57]. On 23 July 2022, the MPOX outbreak was officially declared by WHO a public health emergency of international concern (PHEIC). The decision was taken by the WHO Director-General against the background of a rapid increase in the number of cases-over 16,000 in 75 countries [87]. On 11 May 2023, WHO announced that the global MPOX outbreak was no longer considered a public health emergency of international concern (PHEIC), based on the sustained decline in case numbers and the stability of the clinical picture. The Emergency Committee emphasized the need to shift from emergency response to long-term control strategies, including integration of MPOX into national programs for surveillance, vaccination, and research [49]. (Figure 1).

According to WHO data, from 1 January 2022 to 8 May 2023, a total of 87,377 laboratory-confirmed MPOX cases, including 140 deaths, were reported in 111 countries across all six WHO regions (Figure 2). Since the previous report (27 April 2023), 264 new cases (an increase of 0.3%) and 10 deaths had been recorded, with some cases reported retrospectively [80]. Among MPOX cases with available data on sex, 96.2% (77,834 of 80,872) were men, and the median age of patients was 34 years. The distribution by sex and age remained stable throughout the outbreak. Among patients with known age, 1.3% (1,108 of 83,460) were children under 18 years, including 324 cases (0.4%) in children younger than 5 years. Among cases with available information on sexual orientation, 84.1% (25,871 of 30,761) identified themselves as gay, bisexual, or other men who have sex with men (MSM). Despite minor fluctuations, this proportion consistently exceeded 75%, indicating predominant circulation of the virus in this risk group during the outbreak. In cases where data on sexual orientation were unavailable, the high proportion of male patients may also indicate hidden transmission among MSM [80]. The causative agent of the global MPOX outbreak in non-endemic countries was a Clade IIb virus, predominantly lineage B.1, and less frequently A.1. At the same time, in endemic regions such as the Democratic Republic of the Congo and Nigeria, Clade I and Clade IIa viruses continued to circulate [80]. Following the onset of the MPOX outbreak, urgent measures were implemented: surveillance was strengthened, PCR diagnostics expanded, vaccination of risk groups was organized (primarily using MVA-BN), and isolation of patients was introduced [43, 81, 14]. Leading countries launched information campaigns among key communities aimed at counteracting stigmatization, and WHO ensured international coordination [89].

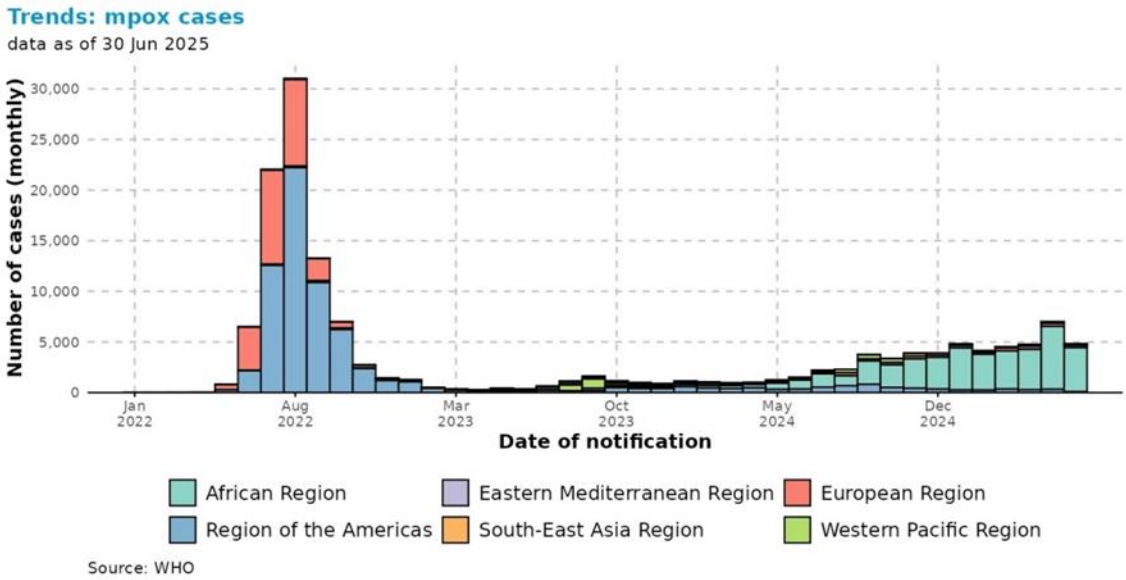

Figure 1. Dynamics of MPOX incidence by world region (January 2022 – June 2025). Source: World Health Organization, 2025, Global Mpox Trends.

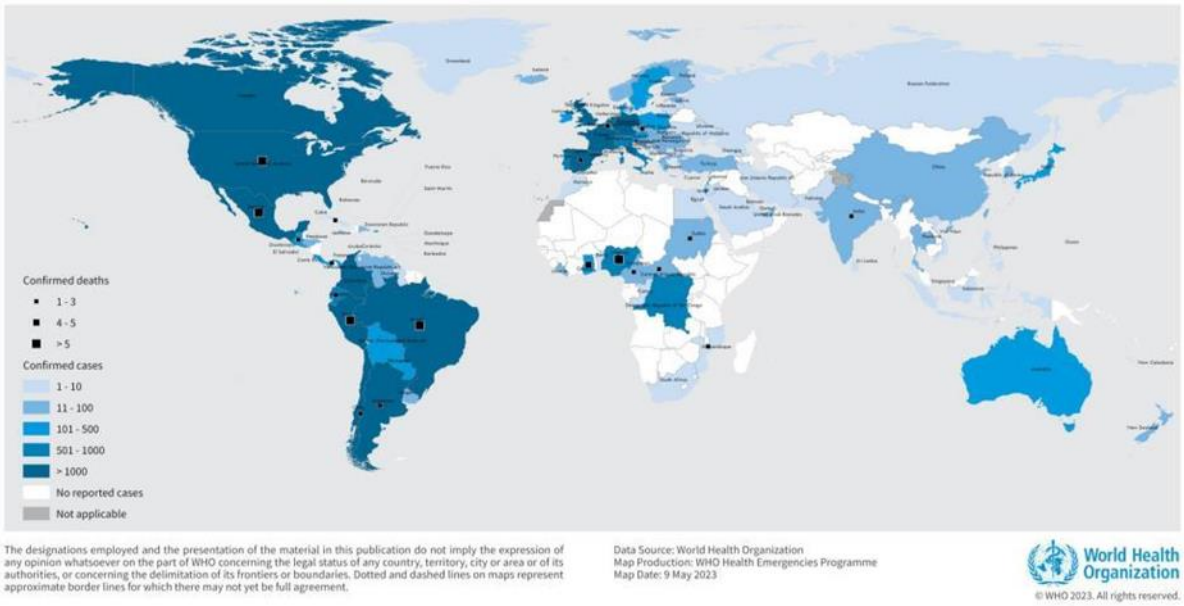

Figure 2. Geographic distribution of confirmed monkeypox cases reported or identified by WHO from official public sources for the period 1 January 2022 to 8 May 2023. Source: World Health Organization, 2023, External Situation Report 22.

In August 2023, the first confirmed MPOX cases were reported in Kinshasa, the capital of the Democratic Republic of the Congo. The index patient arrived by river transport from the endemic province of Maïndombe; his diagnosis was laboratory confirmed on 18 August. Subsequently, infection was detected in several of his close contacts [79]. From 1 January 2024 to 28 July 2024, 13,791 MPOX cases and 450 deaths were reported in the Democratic Republic of the Congo, accounting for 96.3% and 97%, respectively, of all cases and deaths in Africa. Morbidity affected 25 of the country's 26 provinces, with 68% of cases and 85% of deaths occurring in children under 15 years of age. More generally, from 1 January 2022 to 28 July 2024, 37,583 MPOX cases and 1,451 deaths were reported in 15 African Union member states, corresponding to an overall case fatality of 3.9% [3]. During the outbreak, Clade II viruses (including subclade IIa) continued to circulate, and active transmission of a new clade, Ib, more adapted to human-to-human transmission, was documented, predominantly in the eastern part of the Democratic Republic of the Congo. Genomic analysis showed that all investigated MPOX virus isolates obtained during the outbreak in South Kivu Province (eastern Democratic Republic of the Congo) belonged to Clade Ib and formed three distinct clusters. Mutations were identified in viral genomes, predominantly driven by APOBEC3 activity, indicating sustained human-to-human transmission [39]. Against the background of the rapid spread of this new MPOX clade, on 14 August 2024 the WHO Director-General declared the outbreak in the Democratic Republic of the Congo and several African countries a public health emergency of international concern (PHEIC) [86].

As of the period from 1 January to July 2025, MPOX continues to circulate predominantly in African countries. Since the beginning of the year, 30,022 confirmed cases and 119 deaths have been reported in 79 countries, with 28,152 cases and 133 deaths occurring in 24 African countries, accounting for 94% of all global cases. The highest numbers of cases have been recorded in the Democratic Republic of the Congo (13,927), Uganda (6,230), and Sierra Leone (4,876). Despite an overall decline in global incidence, active local outbreaks persist in several regions [83]. Clade Ib viruses dominate in eastern and central Africa, whereas Clade IIb continues to circulate mainly in West Africa and beyond. Isolated imported Clade Ib cases have been reported in Australia, the United Kingdom, and China (Figure 3), confirming the continuing risk of international spread of the infection [73].

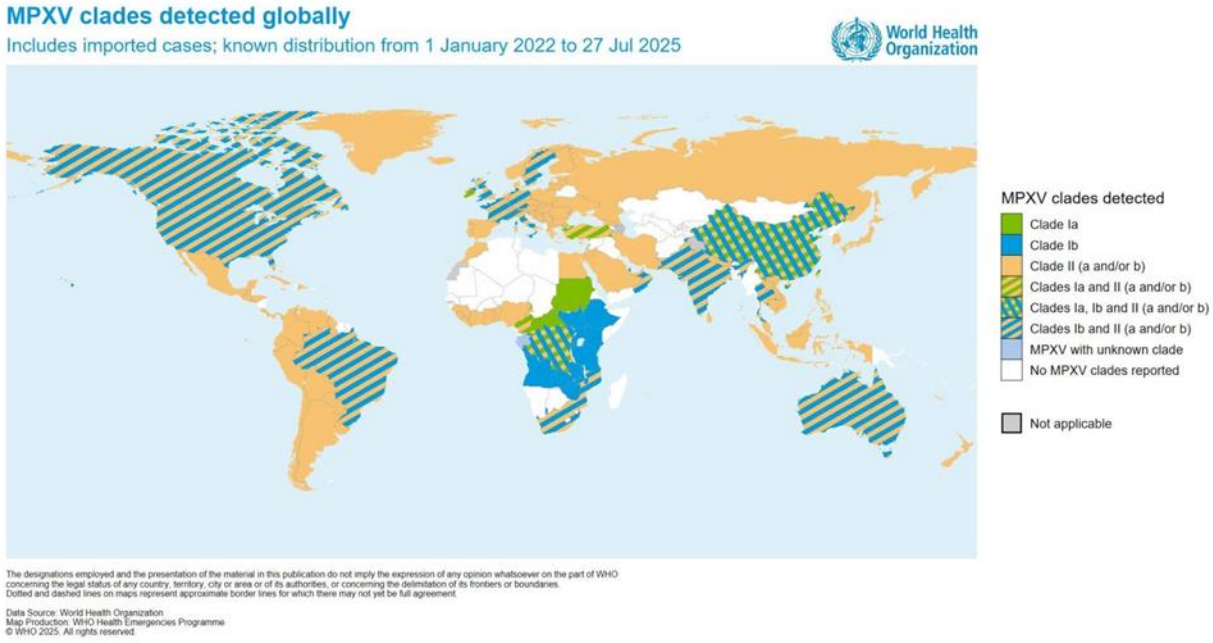

Figure 3. Geographic distribution of monkeypox virus clades, including imported cases, for the period 1 January 2022 to 27 July 2025.
Source: World Health Organization, 2025, Global Mpox Trends.

According to WHO data for the period from 1 July 2024 to 30 June 2025, outside Africa MPOX predominantly affected men of working age. The highest incidence was observed in the 30–39 and 18–29 year age groups. Women accounted for only a small proportion in all age categories. After 50 years of age, incidence declined substantially: in the 50–59 year age group, 353 cases were recorded in men and only 13 in women. Among children and adolescents <18 years, 55 cases were reported over the entire observation period (Figure 4) [73].

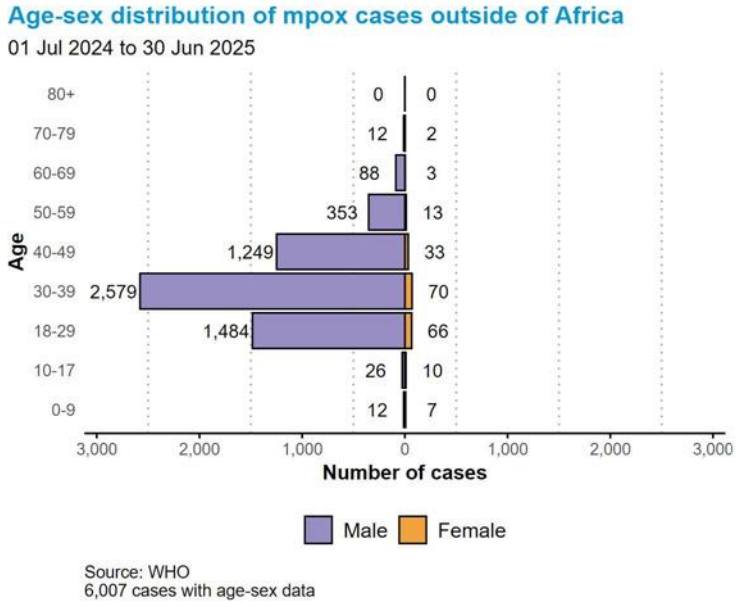

Figure 4. Distribution of confirmed MPOX cases by sex and age outside Africa for the period 1 July 2024 to 30 June 2025.
Source: World Health Organization, 2025, Global Mpox Trends.

In the endemic provinces of the Democratic Republic of the Congo, the epidemiological profile of MPOX cases differs from that observed outside Africa. According to data for the period from 1 January 2024 to 25 July 2025, cases of infection were registered in all age groups (Figure 5). Particularly high incidence was observed among children and adolescents: the 5-9, 10-14, and 15-19 year age groups showed the largest numbers of reported cases. In contrast to the pattern in non-endemic countries, where MPOX predominantly affected men, in the DRC the sex distribution is more balanced-the proportions of men and women are approximately equal in most age groups. A substantial number of cases was also noted in the 20-39 year age group, with a gradual decline in incidence with increasing age. The lowest number of cases was recorded among individuals older than 45 years [73].

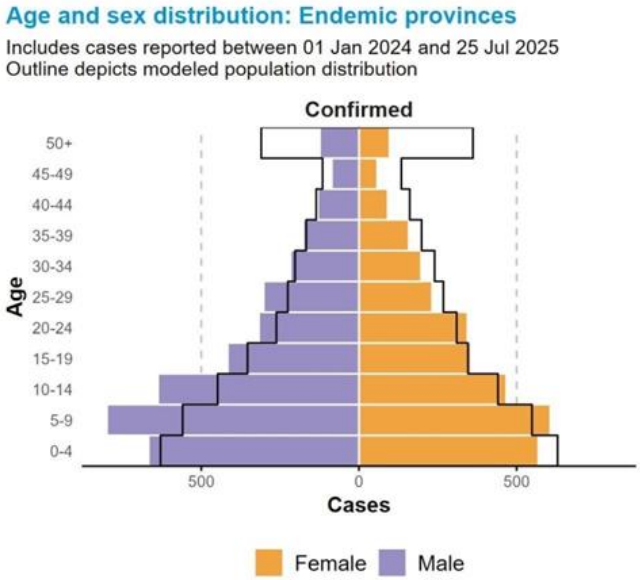

Figure 5. Distribution of confirmed MPOX cases by sex and age in the endemic provinces of the Democratic Republic of the Congo for the period 1 January 2024 to 25 July 2025. (Endemic provinces include: Equateur, Sankuru, Tshuapa, Tshopo, Nord-Ubangi, Bas-Uélé, Sud-Ubangi, Mongala, Kwilu, Maïndombe, and Maniema) Source: World Health Organization, 2025, Global Mpox Trends.

Vaccines

Although immune memory after smallpox vaccination is long-lasting and provides cross-protection, the first two generations of vaccines have critical drawbacks: replicating VACV strains occasionally cause severe complications in individuals with immunodeficiency, eczema, and in transplant recipients; first-generation products also had problems with production standardization. The spread of MPXV beyond endemic regions and the large number of people without residual immunity make it necessary to develop safer, standardized platforms with comparable immunogenicity.

*Classification of vaccine platforms (*Table 1).

Dryvax®, APSV®, Lancy-Vaxina®, and L-IVP® belong to first-generation vaccines (produced before the 1970s-1980s) and contained live vaccinia virus in various pharmaceutical forms-lyophilized, “frozen-liquid,” and calf-lymph [35]. Despite differences in manufacturing technology and type of substrate, all of these products demonstrated comparably high clinical efficacy: the development of the characteristic “take” served as a universal empirical correlate of protection and was accompanied by pronounced humoral and cellular responses that ensured long-term immune memory. At the same time, differences in production approaches led to lot-to-lot variability and affected safety: whereas Dryvax® and L-IVP® were characterized by relatively stable immunogenicity, calf-lymph vaccines (Lancy-Vaxina®) were more frequently associated with technological heterogeneity and a risk of contamination. Overall, all replicating products were associated with frequent mild reactions (≈5-80%) and rare but clinically significant complications: fatal outcomes ≈1-2 × 10^{-6}, postvaccinal encephalitis ≈3-9 × 10^{-6}, eczema vaccinatum ≈2-35 × 10^{-6}, generalized vaccinia ≈40–200 × 10^{-6}; in later series, myopericarditis was reported with a frequency on the order of 10^{-4}. Thus, despite their high efficacy, differences in standardization and safety rendered these vaccines poorly suited to modern mass immunization programs, which in turn led to the development and introduction of second- and third-generation vaccines-cell culture-based and non-replicating-aimed at improving safety while maintaining immune protection [35].

Second-generation vaccines retained the same biological basis-VACV strains close to the original ones-but shifted production to controlled cell culture systems and introduced purification and standardization (e.g., ACAM2000, Elstree-BN). This improved product quality and predictability; however, it did not fundamentally change the risk associated with replication of the vaccine virus: second-generation replicating vaccines still have limitations in use among vulnerable groups and require a cautious approach to mass immunization. ACAM2000, produced in MRC-5 cells and administered as a single dose using a bifurcated needle, demonstrates high seroconversion (≈94-97%) and proven protection in preclinical models and retrospective studies. However, it retains the typical risks of a replicating platform-the possibility of transmission of the vaccine virus and contraindications in children, pregnant women, and immunocompromised individuals (rate of serious adverse events ≈20.25 per 100,000) [18, 71, 55, 28, 41, 42, 35].

Table 1.

Comparative characteristics of vaccine platforms against MPOX.

Vaccine / platform	Type	Regimen and dose of administration	Immunology (seroconversion / NT_{50} / T-cell)	Efficacy / protection (key results)	Risks / safety	Development status
Dryvax®, APSV®, Lancy–Vaxina®, L-IVP®	Live replicating VACV (1st generation)	1 dose, ≈15 punctures, ~10^6–10^8 PFU/mL, scarification	Robust humoral and cellular responses; "take" as an empirical correlate	High historical clinical effectiveness	Frequent mild reactions (≈5–80%); rare serious complications (mortality ~1–2×10^{-6}; encephalitis 3–9×10^{-6}; eczema vaccinatum 2–35×10^{-6}; myopericarditis ~10^{-4})	Historical (withdrawn from widespread vaccination)
ACAM2000	2nd generation, replicating	1 dose, ≈15 punctures, ≈0.0025 mL × 2.5–12.5 × 10^5 PFU, scarification	Seroconversion ≈94–97% in clinical series	Demonstrated protection in retrospective data/model studies	Retains replication-related risks (possibility of transmission; contraindicated in children, pregnant individuals, and the immunocompromised); serious reactions ≈20.25/100,000.	Licensed / in strategic stockpiles
MVA-BN (JYNNEOS / IMVANEX)	3rd generation, non-replicating MVA	2 doses, 0.5 mL, ≈10^8 $TCID_{50}$, subcutaneous (SC)	Seroconversion ≈89% after 2 doses; effectiveness in meta-analysis ~82% (95% CI 72–92%) for the two-dose regimen; one dose ≈76% (64–88%).	Reduction in clinical disease during the outbreak; good tolerability	High safety profile; can be used in individuals with contraindications to replicating vaccines	Licensed; included in stockpiles and recommendations
LC16m8	3rd generation, attenuated partially replicating	1 dose, 0.5 mL, ≈1.5×10^4–10^5 PFU, scarification	Seroconversion ≈70–72% by day 28 after 1 dose	Protection after a single dose in historical/field data	Partial replication → earlier immune response, but caution required in immunocompromised individuals	Licensed in Japan; used in emergency situations
dBTF (Tiantan-derived attenuated)	Replicating, genetically attenuated	Not applicable (preclinical study)	High binding and neutralizing titers; enhancement of cGAS/STING and IFN response	A single vaccination produced a marked reduction in clinical burden: on day 10, control macaques had hundreds of lesions (452, 156, 75), while vaccinated animals had 6, 5, and 1; plasma/tissue viral loads were reduced; NT_{50} values correlated with protection.	Replicating candidate — regulatory risks for immunocompromised individuals; requires thorough safety evaluation.	Advanced preclinical stage (NHP), no clinical data
BNT166 (multi-antigen mRNA-LNP)	Non-replicating mRNA-LNP	Not applicable (preclinical study)	High seroconversion; strong $CD4^+$/$CD8^+$ responses; NT_{50} correlate with protection	In NHP, BNT166 provided 100% prevention of death and suppression of skin lesions under a Clade I challenge	Expected safety of the mRNA platform; needs clinical confirmation	Early clinical trials (phase I/II, NCT05988203)
SpyCatcher003-mi3 VLP (Belghith et al.)	Non-replicating VLP	Not applicable (preclinical study)	Very high NT_{50} (in mice and NHP); in macaques VLP NT_{50} ≈2× higher than JYNNEOS; strong humoral and adequate cellular response	Complete protection in mouse models; in NHP higher NT_{50} values than JYNNEOS; passive transfer of serum from VLP-vaccinated macaques provided better protection in mice than serum from JYNNEOS recipients	High safety (no genome); manufacturing and large-scale trials are necessary	Predominantly preclinical (small NHP groups); no clinical data

Third-generation vaccines represent a transition from replicating viral platforms to safer and more technologically controlled solutions, where the key goal is to reduce the risk of adverse reactions while maintaining adequate immunogenicity. Two of the most illustrative examples are MVA-BN (a non-replicating modified Ankara platform) and LC16m8 (an attenuated temperature-sensitive VACV strain. Both vaccines have inherited the cross-protection characteristic of classical smallpox vaccines, but differ in their biological properties as well as in their practical use profile. MVA-BN, which is unable to replicate in human cells, demonstrates the best safety profile: it does not cause vaccine viremia and can be used in individuals with contraindications to replicating vaccines. According to clinical observations, two doses of the vaccine induce seroconversion in ≈89% of previously unvaccinated individuals and provide protective effectiveness of about 82% (meta-analysis: 82%, 95% CI 72-92%); the effectiveness after a single dose in one review was estimated at approximately 76% (95% CI 64-88%) [50]. LC16m8, by contrast, retains a limited ability to replicate, which promotes more pronounced early activation of the immune response-according to Japanese trials, seroconversion reached 70-72% by day 28-but at the same time requires greater caution in immunocompromised and pregnant individuals. With comparable overall tolerability, LC16m8 is somewhat inferior to MVA-BN in terms of safety profile, but potentially induces a broader cellular response due to preserved, albeit attenuated, replication. Thus, both platforms reflect different strategic approaches: MVA-BN is aimed at maximizing safety and universality of use, whereas LC16m8 seeks a compromise between immunogenicity and controlled replication, which may be important for target groups at high risk of infection [1, 22, 23]. Differences in seroconversion levels between LC16m8 and MVA-BN partly reflect not only the biology of the platforms themselves but also the specifics of study design. LC16m8 was evaluated after a single dose with a relatively short follow-up period (28 days), whereas MVA-BN studies focused on a two-dose regimen with a longer evaluation interval (≈90 days). In addition, serological testing methods and cohort compositions also differed. Consequently, the higher seroconversion observed for MVA-BN in certain series appears to be related to differences in vaccination regimens and time points of measurement rather than necessarily to a fundamental advantage of the platform [71, 21, 17, 6, 63, 65, 21, 17, 51, 75, 84, 44].

An experiment in a black-tailed prairie dog model, in which animals were intranasally infected with an MPXV strain at moderate and extremely high exposure, demonstrated differences in the practical effect of vaccine platforms in post-exposure immunization. In a comparison of the non-replicating MVA-BN (JYNNEOS/IMVAMUNE) and the replicating ACAM2000, both vaccines induced neutralizing antibodies and could delay death when administered after exposure; at the same time, early administration (day 1) of MVA-BN produced more pronounced clinical attenuation compared with administration on day 3, although antibody levels in the different groups were comparable-which likely reflects the specifics of vaccination schedules and timing of measurements. At a very high challenge dose, neither vaccine provided complete protection, underscoring the limited window for effective PEP and the need for prompt intervention. In practical terms, this means that in the PEP setting the non-replicating platform has operational advantages, especially in individuals with contraindications to replicating vaccines [59].

Candidates and promising platforms

The recent attenuated candidate dBTF (Tiantan-derived; deletions J2R/TK, F4L, B2R) demonstrates pronounced single-dose protection in NHP models: a single IM vaccination (2.5×10^5 PFU) led to a significant reduction in the number of skin lesions and viral load at the standard control time point (day 10) and correlated with high NT_{50} values, indicating strong prophylactic efficacy in the acute phase of infection [90]. In parallel, two non-replicating platforms-a multi-antigenic mRNA-LNP vaccine (BNT166) and a nanocage VLP (SpyCatcher003-mi3)-showed comparable protective efficacy in preclinical models but with differing immunological profiles: BNT166 provided complete prevention of death and suppression of skin lesions in mouse and NHP models and has already advanced to early clinical trials (phase I/II), whereas the VLP construct elicited particularly high humoral responses (neutralizing titers in macaques were higher than in JYNNEOS recipients) and excellent passive protection in transmission models but remains predominantly at the preclinical stage and requires large-scale NHP studies to confirm tolerability and long-term durability of the response [93, 8].

Comparing these data reveals clear differences in profiles and translational trajectories: dBTF occupies an intermediate niche between replicating and fully non-replicating platforms-combining enhanced immunogenicity with modified (reduced) replication and a promising safety profile; the mRNA platform (BNT166) shows the advantage of “rapid” clinical translation and a strong multi-epitope T-cell response; the VLP stands out for its particularly potent humoral activity and promise as a safe non-replicating booster. An important methodological remark: direct inter-platform comparison is complicated by differences in models (mice vs CAST vs NHP), challenge doses, endpoints used (death, clinical burden, local replication), and methods for measuring immune correlates (NT_{50}, time points). Consequently, robust ranking of platforms is currently difficult: there are no standardized head-to-head preclinical studies in NHP and no unified clinical trials with harmonized serological and cellular endpoints, nor a systematic assessment of tolerability in vulnerable groups.

Limitations of available data and research needs

Despite promising preclinical and early clinical results for several platforms, the current evidence base on MPXV vaccines has obvious limitations: many studies involve small group sizes (small n), use different formats of neutralization assays and time points of measurement, and there is an almost complete absence of direct comparative (head-to-head) studies, which makes reliable inter-platform comparison difficult. Priority tasks remain the standardization of methods and the search for correlates of protection (including unification of neutralization formats for NT_{50} and harmonization of parameters for assessing T-cell responses), as well as the conduct of large preclinical studies in non-primate species and randomized comparative clinical trials with unified clinical and serological endpoints. In parallel, well-designed observational studies and sustainable pharmacovigilance programs are needed to assess real-world effectiveness and safety profiles in different populations. Only by

combining standardized laboratory methods, large preclinical series, direct clinical comparisons, and systematic post-registration monitoring will it become possible to reasonably rank platforms according to the criteria of "replication-immunogenicity-safety" and make balanced decisions in shaping national vaccination programs and preparedness strategies.

Conclusions

Monkeypox, first described in 1958 in laboratory monkeys, for a long time remained an endemic zoonosis of Central and West Africa [70, 10]. Since the early 2000s, and especially after 2017, imported and localized cases in non-endemic countries have become more frequent, which has led to a reassessment of global risk; the culmination was a large international outbreak in 2022 that affected more than 100 countries and demonstrated the virus's capacity for wide-scale spread [34, 19, 67, 79].

As of July 2025, no confirmed MPOX cases have been reported in Kazakhstan, but the absence of notifications does not exclude the country's vulnerability given its transit position between Europe and Asia and dense transport and trade links with regions where cases have been recorded (including China, the Russian Federation, and European countries) [73, 83]. Additional concern is raised by the Clade Ib variant, which is actively circulating in Eastern and Central Africa, shows signs of enhanced human-to-human transmission, and has already been detected outside the continent (China, the United Kingdom, Australia) [39, 73].

Particularly important from an epidemiological standpoint are vulnerable groups-men who have sex with men (MSM), people living with HIV and other forms of immunodeficiency, as well as sex workers-as confirmed by analyses of the 2022–2024 outbreaks [58, 57, 80]. The 2022–2023 outbreak demonstrated the key role of close skin-mucosal contacts (including sexual) in transmission; at the same time, detection of viral DNA in semen rarely correlates with the presence of replication-competent virus. The routes of MPXV introduction are not limited to human-to-human transmission: zoonotic events (including the 2003 episode in the USA associated with the import of infected rodents) and natural foci involving reservoir animals remain important sources of new outbreaks. The main mechanisms of transmission are direct contact with skin lesions and biological secretions, fomite transmission (linen, clothing, surfaces), and, with prolonged close contact, the droplet-aerosol route; vertical transmission has been described rarely but is possible. Taken together, these data indicate the need not only for control of the trade in wild animals, but also for strengthening surveillance, rapid identification and isolation of cases, as well as targeted communication and preventive measures for high-risk groups [76, 73, 30, 27, 53, 69, 7, 58, 58, 40, 82].

Modern MPOX vaccines are represented by several platforms that embody trade-offs between immunogenicity, safety, and practical accessibility, so the choice should be context dependent. Non-replicating platforms (MVA-BN / JYNNEOS / IMVANEX) are prioritized-they are preferred for PEP and targeted PrEP in risk groups (laboratory and clinical staff, specific population clusters) due to their favorable safety profile and the possibility of use in individuals with contraindications to replicating vaccines [21, 51, 85]; a two-dose MVA-BN schedule provides a more sustained serological response for planned PrEP, whereas a single dose is applicable in an emergency PEP regimen. LC16-KMB may be considered a useful alternative in scenarios where partial replication is acceptable (including some pediatric groups) [75, 84, 85], whereas ACAM2000, despite its high immunogenicity, is appropriate only under strictly limited indications and with careful selection of recipients [41].

At the same time, significant gaps remain in the evidence base: there are insufficient data on effectiveness in different populations and almost no direct comparative studies. Priorities include standardizing assessment methods and identifying correlates of protection, conducting head-to-head and large-scale NHP/clinical trials, as well as clinical validation of promising mRNA, VLP, and attenuated candidates. Until such data accumulate, it is reasonable for national strategies to be built around ensuring access to vaccines and targeted PrEP/PEP programs for high-risk groups, including: (1) priority development and stockpiling of replicating and non-replicating vaccines; (2) rapid PEP protocols for contacts (optimally within the first 4 days); (3) targeted PrEP campaigns for high-risk occupational groups; (4) systematic data collection for subsequent policy adjustment and platform selection.

Thus, despite the absence of registered MPOX cases in Kazakhstan, maintaining epidemiological vigilance, ensuring the functioning of early detection and laboratory confirmation systems, as well as forming strategic vaccine stockpiles and advancing their development, training healthcare personnel, and conducting targeted information and educational activities among high-risk groups remain priority areas for the national biosafety system.

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Corresponding author:
Tuyakov Ayan - Master of Science (Natural Sciences), Junior Researcher, «Limited Liability Partnership «Research Institute for Biological Safety Problems».
Postal address: 080409, Republic of Kazakhstan, Zhambyl Region, Korday District, urban-type settlement of Gvardeyskiy.
E-mail: asemgul.baygazina@bk.ru
Phone: + 87081821679