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# Monkeypox and other orthopoxvirus zoonoses

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**SUMMARY**

The paper highlights the current knowledge on infection biology, epidemiology and evolution of monkeypox virus (MPXV), cowpox virus (CPXV), buffalopox virus (BPXV), camelpox virus (CMLPV), as well as addresses some factors that modulate dynamics of orthopoxvirus transmission, manifestation of orthopoxvirus infections and their preservation in nature. Despite the elimination of the historically infamous smallpox, orthopoxviruses remain a serious veterinary and health problem. Their role is currently increasing while the number of persons not immune to smallpox grows. Along with this, there is a genetic transformation of pathogens. In this regard, the risks of human infection with orthopoxviruses of zoonotic nature are increasing. The problem of monkeypox, cowpox, buffalopox and camelpox and the respective agents included in the genus of zoonotic orthopoxviruses presents the greatest interest. Along with the increased number of human monkeypox cases in 2020–2022, a retrospective analysis of the last 20 years shows that the activity of monkeypox outbreaks in the XXI century intensified in Central African countries. Cowpox outbreaks in Europe and camelpox outbreaks in Southwestern and Central Asia have also become more active. In 2011, in India, the camelpox virus overcame the interspecies barrier and caused a clinical pox-like disease in humans. Scientists are alarmed by these facts as the camelpox virus genome is 99% homologous to the genome of the smallpox virus. This requires strengthening the epizootological and epidemiological monitoring of orthopoxvirus zoonotic pathogens.

**Keywords:** review, monkeypox, cowpox, buffalopox, camelpox, orthopoxviruses, zoonoses

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# Оспа обезьян и другие ортопоксвирусные зоонозы

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**РЕЗЮМЕ**

В представленной работе освещено текущее состояние знаний, касающихся биологии инфекции, эпидемиологии и эволюции вируса оспы обезьян (MPXV), оспы коров (CPXV), оспы буйволов (BPXV), оспы верблюдов (CMLPV), а также некоторые факторы, которые модулируют динамику передачи ортопоксвируса, проявление ортопоксвирусных инфекций и их сохранение в природе. Несмотря на ликвидацию исторически печально известной натуральной оспы, ортопоксвирусы остаются серьезной проблемой ветеринарии и здравоохранения. Их роль в настоящее время возрастает на фоне увеличения количества людей, которые не имеют иммунитета против натуральной оспы. Наряду с этим наблюдается генетическая трансформация возбудителей, что становится причиной роста рисков поражения человека ортопоксвирусами зоонозной природы. Наибольший интерес представляет проблема оспы обезьян, оспы коров, оспы буйволов и оспы верблюдов, возбудители которых входят в род зоонозных ортопоксвирусов. На фоне учащения проявления случаев заболевания человека оспой обезьян в 2020–2022 гг. ретроспективный анализ последних 20 лет показывает, что активность очагов оспы обезьян в XXI в. возрастала в государствах Центральной Африки. Также активизировались очаги оспы коров в Европе, оспы верблюдов в Юго-Западной и Центральной Азии. В 2011 г. в Индии вирус оспы верблюдов преодолел межвидовой барьер и вызвал клиническую оспоподобную форму заболевания у человека. Подобные факты тревожат ученых, так как геном вируса оспы верблюдов на 99% гомологичен геному вируса натуральной оспы. Это требует усиления эпизоотологического и эпидемиологического мониторинга за возбудителями ортопоксвирусных зоонозов.

**Ключевые слова:** обзор, оспа обезьян, оспа коров, оспа буйволов, оспа верблюдов, ортопоксвирусы, зоонозы

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## INTRODUCTION

Why do poxviruses rank high as potential viral threats? This family includes many pathogens that affect both vertebrate (including humans) and invertebrate representatives of the animal kingdom. Despite eradication of the infamously known smallpox, the poxviruses belonging to the genus *Orthopoxvirus* and causing serious zoonotic diseases remain a challenge in veterinary medicine and healthcare. This review summarizes general characteristics of orthopoxviruses, as well as addresses current and future threats posed by these viruses to humans, domestic and wild animals. In-depth studies of this genus' representatives allow expanding fundamental biological knowledge and understanding the methodological approaches to prevention and control of other infectious diseases of zoonotic nature [1].

Currently, there is an increase in the number of humans worldwide that are not immune to smallpox, along with genetic transformation of zoonotic pathogens of orthopoxvirus nature. This increases the risk of infection in humans. Another risk factor is the ability of poxviruses to overcome the species barrier, as it occurred in case of monkeypox virus [2–7]. A retrospective analysis carried out within the last 20 years shows that the activity of smallpox outbreaks in monkeys increased in the XXI century in African countries [8, 9]. Outbreaks of cowpox in Europe [2, 6, 7], buffalopox [4, 10–12, 15] and camelpox in Southwest and Central Asia [13, 14] also intensified. In 2011, in India, the camelpox virus overcame the interspecies barrier and caused a clinical pox-like form of the disease in humans [16–19]. Scientists are alarmed by these facts [20–22], as the camelpox virus genome is 99% homologous to that of the smallpox virus [23]. Multiple mutations were identified in some genes, including the C18L gene responsible for the host species' gene [24].

## GENERAL CHARACTERISTICS OF ORTHOPOXVIRUSES

The family *Poxviridae* consists of two subfamilies: *Chordopoxvirinae* (poxviruses of vertebrates) and *Entomopoxvirinae* (poxviruses of insects). The subfamily *Chordopoxvirinae* is represented by large DNA-viruses of a brick-like or ovoid shape. They are grouped into genera and infect mammals, with the exception of *Avipoxvirus* (infect specifically birds) and *Crocodylidpoxvirus* (crocodiles serve as natural hosts). The genus *Parapoxvirus* is isolated and its members possess a unique spiral envelope that distinguishes them from other poxviruses (Orf virus, bovine papular stomatitis virus and sealpox virus). Agents of molluscum contagiosum and currently eradicated smallpox are the only poxviruses that have humans as their host and reservoir [25].

The best-known is the genus *Orthopoxvirus*, which includes vaccinia virus, as well as monkeypox, cowpox, buffalopox, camelpox viruses and some other orthopoxviruses [25–28].

According to the IX International Committee on Taxonomy of Viruses (ICTV) Report (2012), the genus *Orthopoxvirus* included 11 virus species (see the Table).

The taxonomy of the genus *Orthopoxvirus* is constantly updated. In the XXI century the new representatives of orthopoxviruses were detected in North America – *Skunkpox virus* (SKPV), and in Africa – *Uasin Gishu disease virus* (UGDV), which was named after the Kenyan province. In 2010, 2015 and 2017 three more new members of the genus *Orthopoxvirus* were identified in Georgia (Akhmeta and Van regions), USA (Alaska) and Italy: *Akhmeta virus*, *Alaskapox virus*, and feline poxvirus, respectively [29–32]. The emergence of mutated animal orthopoxviruses that are similar to the smallpox virus cannot be excluded [33].

In 2018, foreign researchers developed the first complete synthesis of a horsepox virus, the work results were published in the *PLoS ONE* [34].

To date, complete nucleotide sequences of orthopoxviruses genome have been determined – they are deposited in the GenBank international database. It should be noted that the first full-genome sequencing of the smallpox virus isolated in India in 1967 was carried out by researchers of the State Scientific Centre of Virology and Biotechnology "VEKTOR" [35–40]. Babkin I. V. determined the nucleotide sequence of hemagglutinin and fusion protein genes for various strains of the genus *Orthopoxvirus*. To develop molecular methods for the diagnosis and differentiation of orthopoxviruses, they were offered to use the sequence of the A27L gene encoding a conserved virion protein [26].

The divergence of poxviruses from the original virus and separation into modern genera began about 500 thousand years ago. The *Orthopoxvirus* progenitor might emerge about 300 thousand years ago. Gradually, various species began to emerge within the genus (Fig. 1) [23, 24]. Calculations showed that species evolutionarily close to the smallpox virus – camelpox virus and taterapoxvirus – separated from a common ancestor (apparently rodent virus) about (3.4 ± 0.8) thousand years ago. In the process of evolution the genus *Orthopoxvirus* split into two main branches. At the same time, the genetic picture of evolution is very diverse and differs significantly for individual orthopoxviruses [23, 24, 33, 41, 42].

Orthopoxviruses multiply in cell cytoplasm, and there are several stages of replication in the cells of infected animals that are described in detail and are practically the same for different representatives of the genus [43–45].

These viruses are sensitive to various disinfectants, including solutions of 1% sodium hypochlorite, 1% sodium

**Table**
**Classification of orthopoxviruses** [29]

| Members of the genus *Orthopoxvirus* based on taxonomy of viruses | | | |
|---|---|---|---|
| 1991 | | | |
| *Variola virus* (VARV); *Monkeypox virus* (MPXV); *Cowpox virus* (CPXV); *Camelpox virus* (CMLPV); *Ectromelia virus* (ECTV); *Vaccinia virus* (VACV) (subspecies: *Buffalopox virus*, *Rabbitpox virus*); *Raccoonpox virus* (RCN); *Taterapox virus* (TATV) | | | |
| | 1995 | | |
| | *Volepox virus* (VPXV) | | |
| | | 2000 | |
| | | *Uasin Gishu disease virus* (UGDV) – named after the Kenyan province, affects horses* | |
| | | | 2010 |
| | | | *Skunkpox virus* (SKPXV) |
| Total 8 species | Total 9 species | Total 10 species | Total 11 species |

* not been approved as species.

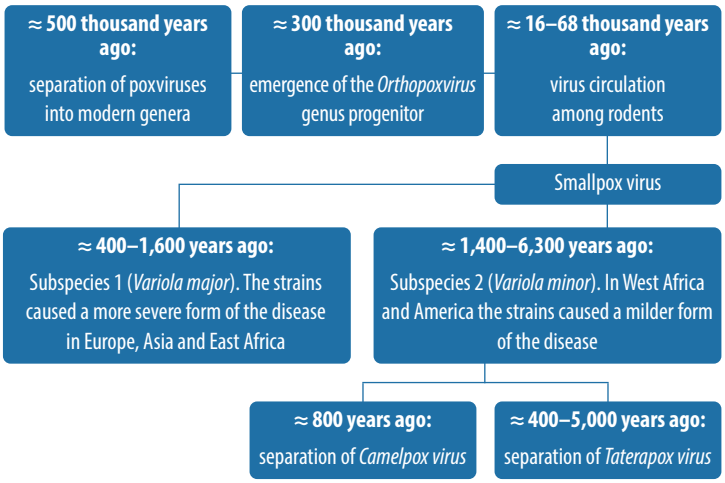


*Fig. 1. Evolution of poxviruses (based on [33])*

hydroxide, 1% peracetic acid, formaldehyde, 0.5–1% formalin and 0.5% quaternary ammonium compounds. They are destroyed by autoclaving or boiling for 10 minutes, as well as if exposed to ultraviolet light [39, 46].

It is believed that the monkeypox, cowpox, buffalopox and camelpox viruses are genetically similar, might infect humans and induce cross-immunity [26–28].

## MONKEYPOX

Some infectious diseases occurring in monkeys pose a danger to humans and other animals [47–51].

Monkeypox is a zoonotic disease caused by the monkeypox virus (MPXV) (Fig. 2), genome of which is represented by double-stranded DNA. MPXV belongs to the family *Poxviridae*, the genus *Orthopoxvirus* [48].

This disease is endemic in some Central and West African countries. The circulation of the virus among wild animals was established, monkeypox cases were recorded in humans in Africa and countries outside the African continent [52–53].

The natural MPXV reservoir and transmission mechanism have not been definitively identified. Infection occurs aerogenically (by airborne droplets), orally, via damaged skin. Diseased primates (12 species), virus-infected humans, rodents are the sources of infection [52]. The disease is characterized by intoxication syndrome, vesicular-pustular rash on skin and mucous membranes [48]. Unfortunately, the collected data on this disease in monkeys are limited and scattered.

The pathogen was first isolated in 1958 at the State Serum Institute in Copenhagen from a crab-eating macaque with pustular rashes on the skin, and designated as a monkeypox virus [54, 55].

The virus is contagious, causes disease in almost all simian species and can infect other animals, such as ground squirrels (*Spermophilus tridecemlineatus*), black-tailed prairie dogs (*Cynomys ludovicianus*), Kellen's dormouse (*Graphiurus kelleni*), mice, steppe marmots (*Marmota bobak*). In Africa, MPXV is found in many animal species, such as striped squirrels, tree squirrels, Gambian rats, striped mice. The pathogen immunologically cross-reacts with other orthopoxviruses, but has specific antigens that are detected using monoclonal antibodies. The monkeypox clinical picture varies in different simian species. The disease is most severe in orangutans. Green monkeys develop a disease of moderate severity; rhesus macaque, hamadryas baboons and chimpanzees have a mild form of infection. The incubation period in animals experimentally infected parenterally ranged from 3 to 8 days [54].

In natural conditions the incubation period lasts 10 days. The disease begins acutely: the temperature rises, cough develops, lethargy and loss of appetite are observed. Generalized lymphadenopathy often develops by the end of the first week, lasting up to 3 weeks. At day 3–14 papular rashes are found on the skin and mucous membranes, undergoing ulceration with spread to the lips, eyelids, mucous membranes of the mouth and pharynx. Later, a papule turns into a pustule. The crusts are formed and disappear on day 21, scars appear. Mortality ranges from 3 to 40% (in orangutans) [27, 50, 55].

Laboratory diagnosis is based on molecular biological (PCR), immunochemical (various modifications of ELISA), virological (virus isolation in cell culture, using the chorioallantoic membrane of chicken embryonated eggs and laboratory animals) and serological test methods. It is advisable that personnel working with monkeys, especially those animals arriving during the quarantine period, should be vaccinated against monkeypox [48, 50, 55].

The monkeypox virus is not an evolutionary progenitor of the smallpox virus, but it is also considered dangerous for humans [48, 56]. At the end of the XX century monkeypox rarely occurred in humans, but in the 2020s the frequency and geographical distribution of infection cases in humans increased [57, 58]. Monkeypox was first diagnosed in a traveler from Nigeria in the USA in 2001 [59], and some more cases were identified in 2003. A prairie dog was identified as the source of infection [60].

In September 2017 a major outbreak of human monkeypox occurred in Bayelsa State (Nigeria) [61]. During the examination of 21 diseased people the following clinical signs were recorded: skin rash – 100% of cases, fever – 80.1%, itching – 66.7%, malaise – 61.9%, lymphadenopathy – 61.9%, chills and sweating – 61.9%, headache – 57.1%, oral sores – 52.4%, genital ulcers – 41.6%, sore throat – 42.8%, myalgia – 23.8%, pain – 23.8%, cough – 19.0%, conjunctivitis – 19.0%, nausea and vomiting – 14.3%, sensitivity to light – 14.3%, hepatomegaly – 9.5%, dehydration – 9.5%, vulvar swelling – 9.5%, poor appetite – 9.5%, tongue sores – 9.5%, scrotal swelling – 9.5%, diarrhea – 4.8%. This outbreak and the subsequent export of the virus with travelers from Nigeria to other parts of the world in 2018–2020 caused serious concerns of scientists who assumed that MPXV could occupy the ecologic and immunological niche left vacant by the smallpox virus [61, 62].

The clinical picture caused by MPXV in humans is similar to that of smallpox, but they differ epidemiologically [56]. Vaccination against smallpox protects people from monkeypox. Human-to-human transmission of the virus was reported [52].

Skin lesions of a monkeypox affected patient are shown in Figures 3, 4.

According to the WHO, by mid 2022 the number of people infected with monkeypox virus exceeded 3.4 thousand people in 50 countries of the world. More than 86% of all infected individuals were residents of European countries [63].

The MPXV biological properties were studied using non-human primates, prairie dogs, African squirrels, ground squirrels and immunodeficient mice [64]. Virus titration in prairie dogs showed that Congo Basin clade MPXV isolates are more virulent via intranasal route than West African MPXV isolates [65]. According to A. A. Sergeev et al., steppe marmot are the most sensitive to the monkeypox virus, while rabbits and guinea pigs intranasally challenged with suspended Congo Basin MPXV V79-1-005 strain did not demonstrate any observable signs of the disease. The results of this work suggested that steppe marmots could be used as model animals for studying the properties of this virus [64, 66].

Thus, MPXV is the causative agent of monkeypox. The disease is similar to smallpox as regards its clinical manifestations. The virus is mainly detected using laboratory diagnosis methods. Current epizootological monitoring of monkeys and other susceptible animals is necessary due to the fact that monkeypox is recognized as the most important orthopoxvirus infection in humans in the era following smallpox eradication [54, 66, 67].

## COWPOX

Until the 1970s it was believed that cowpox virus (CPXV) causes outbreaks only in cattle population, demonstrating clinical signs that are more often manifested in the form of local (lesions on the skin of the udder and on the nipples), more rarely systemic infection (which is more typical for calves). Later it was found out that a much wider range of animals are susceptible to the virus; moreover, CPXV is pathogenic to humans and can cause systemic infection in people with weakened immune status [21, 22, 24, 44, 68].

The causative agent of cowpox is a DNA poxvirus with complex symmetry, belonging to the *Poxviridae* family, the genus *Orthopoxvirus*, the *Cowpox virus* species (clades Brighton Red – CPXV-BR, GRI-90-CPXV-GRI) [68].

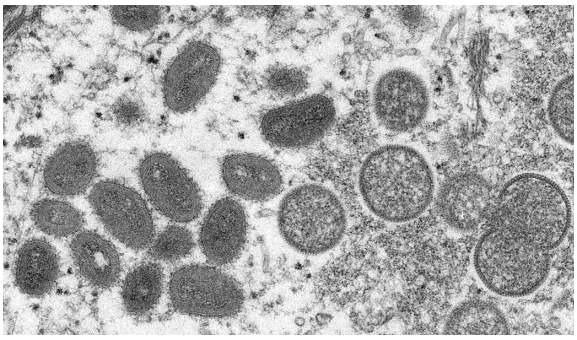

*Fig. 2. Monkeypox virus (https://nashpoz.ru/wp-content/uploads/2022/05/2022-05-19T105043Z_1152629469_RC2T9U9TZXD0_RTRMADP_3_HEALTH-MONKEYPOX-PORTUGAL-SPAIN.JPG.jpg)*

The virus propagates well in the chorioallantoic membrane of chicken embryonated eggs, forming plaques, and in certain cell cultures (Vero, MRC-5, RK13, etc.), inducing a cytopathic effect [69].

CPXV replication in cutaneous cells of infected animals goes through a number of stages described in detail and practically indistinguishable from other orthopoxviruses [70–73].

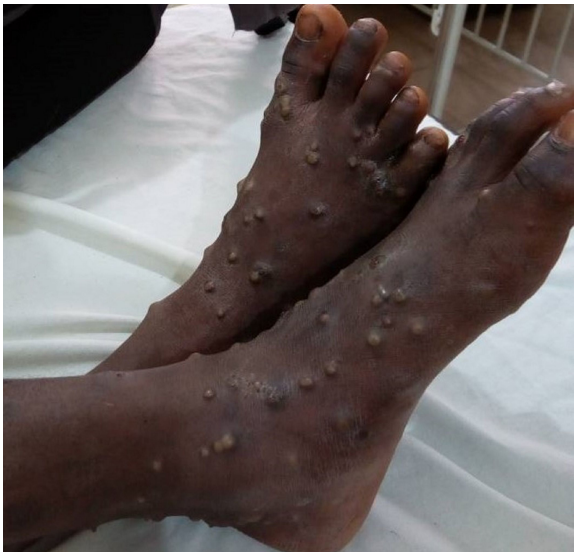

*Fig. 3. Vesicular-pustular lesions on feet of monkeypox affected patient [61]*

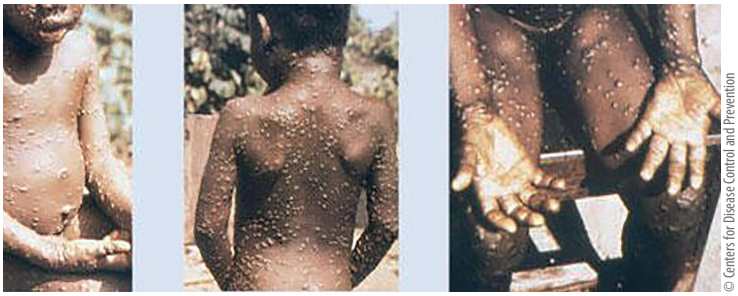



*Fig. 4. Child with monkeypox virus infection*

The clinical signs of cowpox in different animals are quite similar, regardless of the infected species, and are mainly manifested as skin damage. The virus is epitheliotropic, the disease often starts with the appearance of vesicular lesions, that later develop into a pustule with a depressed center.

CPXV lesions in humans are usually localized and self-limiting, but can lead to mortality in patients with immunosuppression [74, 75].

The study of the ecology of cowpox virus revealed that this pathogen spread among laboratory and wild rodents in natural biocenoses [70, 76–79]. High antibody titers detected in felines (family *Felidae*) and some other carnivora indicate a high infectivity of this virus. Outbreaks caused by CPXV were reported in lions, leopards, cheetahs, snow leopard, bush dog, banded mongoose (*Mungos mungo*) and jaguarundi (*Herpailurus yagouaroundi*), as well as elephants, rhinoceroses, camels in zoos and circuses [80–83]. Mortality among exotic animals and felines is high, although no exact data are available. Exotic zoo animals can get infected if they are kept in close proximity to other animals that come into contact with wild rodents [75].

Numerous data on CPXV and its antibodies detected in wild rodents allowed D. K. Lvov [68] to make an assumption about the leading role of these animals as the main reservoir of cowpox. Wild rats can be either a primary reservoir or a reinforcing host [75, 79, 84].

Cowpox virus shows environmental stability. It survives at low temperatures, in crusted scabs, in glycerin. The virus-containing material subjected to heat treatment is inactivated within a few minutes and it is relatively resistant to disinfectants [85].

Diseased animals and virus carriers are the source of the pathogen. Cowpox virus enters the body via aerogenic or alimentary route during contact of diseased and healthy animals via damaged skin and mucous membranes (udder, nipples, scrotum, head, neck, thighs).

The clinical signs of the disease have been specified in detail for cattle (Fig. 5). The disease is most commonly manifested as mastitis associated with reduced milk yield and lactation [85].

Animals recover in 3–4 weeks if no complications occur, and the disease is delayed for 1.5–2.0 months in case of complications. Adult animals generally have a mild form of disease. Calves develop bronchopneumonia and gastroenteritis.

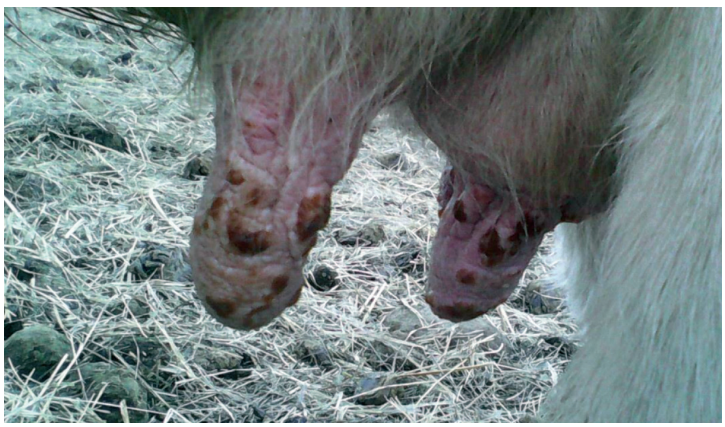

*Fig. 5. Affected udder nipples [86]*

The virus penetrates blood, lymph nodes and internal organs. The viremia is accompanied by increased body temperature, depression. Convalescent cows develop lifelong immunity [85].

Reports on human cowpox cases appeared in the XVIII century. Cowpox was considered an occupational disease of milkers. The disease in humans is generally benign, but complications may occur in unvaccinated persons and individuals with weakened immunity. In rare cases systemic infection or death are observed [40]. Natural CPXV isolates that are poorly studied or not studied at all are potentially dangerous [66, 70, 87]. In the future, the frequency of human infection may increase [75].

In 2008, four individuals were infected with cowpox virus in Krefeld (Germany). The CPXV HumKre08/1 virus was isolated. CPXV-infected rats from a pet store were a source of infection. All animals died. In the same year, another infection case was diagnosed – cowpox virus was isolated from an employee of a private reptile zoo in Landau (Fig. 6), it was named CPXV HumLan08/1.

The HA gene sequence of both virus strains turned out to be different. Figure 7 shows the evolutionary relationships of orthopoxvirus isolates recovered during the specified outbreaks and reference orthopoxvirus strains [75].

Cowpox virus played a certain role in the specific prevention of smallpox in humans. In 1796 E. Jenner developed a method of vaccination against this disease by inoculating CPXV to humans [88].

At present, CPXV should be considered as a rodent virus – zoonosis with natural nidality. Human infection is possible through contact not only with diseased cows, but also with any infected animal. The risk of cowpox outbreaks is high. Epizootological and epidemiological monitoring is required [68, 75, 79, 84].

## BUFFALOPOX

Buffalopox is a contagious viral disease affecting buffaloes (*Bubalus bubalis*) and, less often, cows. Information on this infection is systematized in the review by S. V. Borisevich et al. [15]. The disease is zoonotic. Humans (mainly nursing staff and milkers) get infected from animals.

The causative agent is the vaccinia virus.

Till 5 to 80% of buffaloes get diseased during outbreaks. The incubation period lasts 2–4 days. The disease clinical manifestations include pox sores on the udder, nipples, eyelids, in the groin area, on the scalp. Severe forms occur in association with systemic rash. In 10 days the sores resolve with scab formation. There might be complications: eye swelling and bulging, corneal ulcer, ear discharge. Recovery occurs within 1–2 months. Transmission of the virus from animal to animal occurs through milkers, however, there is no confirmed data on human-to-human infection yet [89–91]. The disease does not cause a high mortality among animals, but results in decreased productivity, milk yield reduction and trade restrictions. Outbreaks are reported in countries where buffaloes are bred as dairy cattle [89, 90].

For the diagnosis and differentiation of the buffalopox virus, methods of viral isolation, modern test systems for the virus detection, including a polymerase chain reaction based on buffalopox virus (C18L) specific gene, and methods for determination of specific antibodies were developed [92].

The incubation period in humans infected with buffalopox virus lasts 3–19 days. Lesions occur on the fingers or forearms and, as a rule, are accompanied by a mild fever, which begins on day 1–4 and lasts 4–5 days. Recovery occurs within 2 weeks [90]. There is an assumption that the buffalopox virus became pathogenic for animals and humans due to adaptive evolution [15, 89, 93].

The possibility of VACV interspecies transmission, including cows, buffaloes and humans, implies potential reoccurrence of the virus and emergence of new outbreaks. Epizootological and epidemiological monitoring is necessary [92, 94].

## CAMELPOX

Camelpox is a zoonotic contagious disease that occurs with the formation of typical cutaneous and mucosal nodular-pustular smallpox lesions. Camelpox virus (CMLPV) belongs to the family *Poxviridae*, the genus *Orthopoxvirus* [95].

The disease is recorded on almost all continents where camel husbandry is practiced except Australia (where the dromedary camel was introduced in the XIX–XX centuries) and South America (where lamas and related species are considered livestock animals) [95–97]. Serological tests showed a high prevalence of CMLPV antibodies [98].

The nucleotide sequence analysis showed that CMLPV is most related to the smallpox virus. Vaccination of camels with vaccinia strains showed good results.

Camelpox virus multiplies in cell cultures (Vero, MA-104, MS, BHK, camel skin) and in primary cell cultures (lamb testicles, lamb kidneys, camel embryo kidney, calf kidneys, chicken embryo fibroblasts) [99, 100], hemagglutinates cockerel erythrocytes [99], is stable at pH of 5–8.5.

The incubation period lasts 9–15 days. Camelpox clinical manifestations vary from mild smallpox lesions localized on skin to moderate and severe lesions with systemic infection. It might depend on the CMLPV strain or the immune status of animals [98]. Skin lesions appear on day 1–3 after the onset of fever: first erythematous spots, papules and vesicles, and then pustules that turn into crusts, localizing on eyelids, nostrils and ear edges. They can spread to neck, limbs, genitals, mammary glands and perineum. Lymph nodes get enlarged. In case of systemic disease, lesions are found on the mucous membranes of the mouth and respiratory tract, sometimes blindness is observed [98, 101–103].

Recovery occurs in 4–6 weeks. Pregnant cows might abort. Mortality is usually associated with secondary infections and septicemia [30, 96, 98].

Transmission of the pathogen occurs via contact with infected animals in a contaminated environment. The route of infection is aerogenic or through abrasions on the skin. The virus is shedded with milk, saliva, and discharge from the eyes and nose. Dried scabs formed during smallpox infection may contain a live virus for at least 4 months and contaminate the environment [97].

Immunity against camelpox is both antibody- and cell-mediated. It is considered that circulating antibodies are not indicative of the animal's immune status [98]. Lifelong immunity is acquired after natural infection. A live attenuated vaccine gives protection against the disease for 6 years [104].

The camelpox virus is species-specific and does not infect other animals, including cattle, sheep and goats [18, 102].

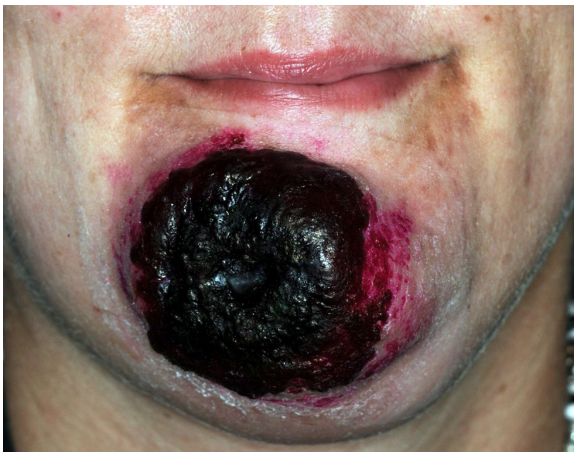

*Fig. 6. Patient affected by cowpox virus strain CPXV HumLan08/1 [75]*

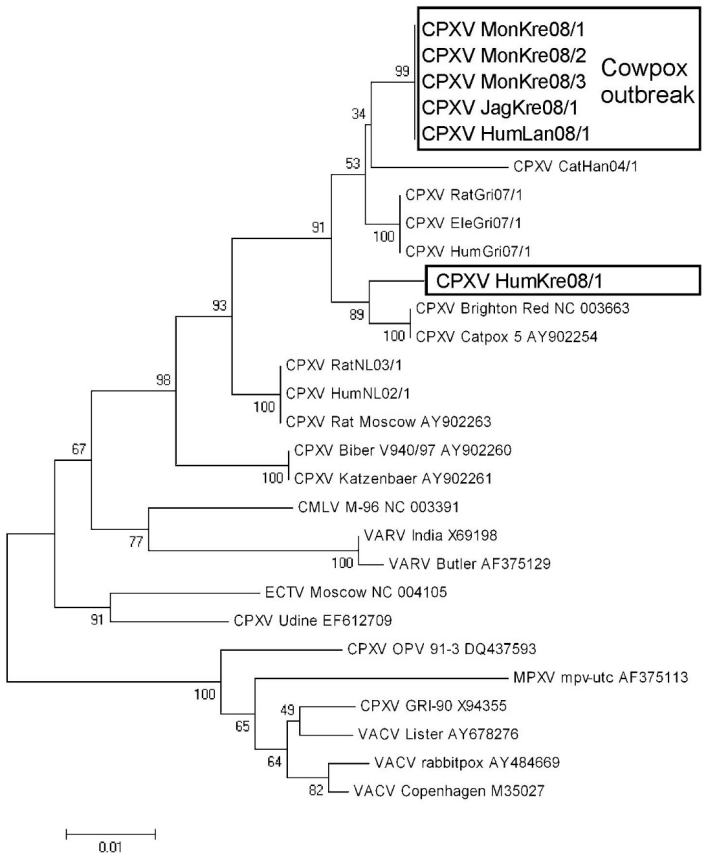


*Fig. 7. Evolutionary relationships of orthopoxvirus recovered isolates and reference strains [75]*

## CONCLUSION

Along with the increased number of human monkeypox cases in 2020–2022, measures are required to strengthen epizootological and epidemiological monitoring of zoonotic orthopoxviruses.

Outbreaks of orthopoxvirus infections make it urgent to develop reliable and species-specific rapid methods for detecting relevant pathogens, to expand the panel of DNA samples of orthopoxviruses and include fowlpox virus, rabbit myxoma virus, chickenpox virus, herpes simplex virus type I and II.

Epizootological and epidemiological issues, molecular and biological mechanisms of virus replication and virus-host interaction should be considered prospective research developments within orthopoxvirus studies.

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