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CME ARTICLE

Poxvirus infections in dermatology – the neglected, the notable, and the notorious

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Summary
The family *Poxviridae* currently comprises 22 genera that infect vertebrates. Of these, members of the *Ortho-*, *Para-*, *Mollusci-* and *Yatapoxvirus* genera have been associated with human diseases of high clinical relevance in dermatology. Historically, smallpox had been a notorious health threat until it was declared eradicated by the World Health Organization in 1979. Today, dermatologists are confronted with a variety of poxviral infections, such as farmyard pox, which occurs as a zoonotic infection after contact with animals. In the tropics, tanapox or vaccinia may be in the differential diagnosis as neglected tropical dermatoses. Molluscum contagiosum virus infection accounts for significant disease burden worldwide and is classified as a sexually transmitted infection in certain scenarios. Recently, mpox (monkeypox) has emerged as a public health emergency of international concern, requiring rapid recognition and appropriate management by dermatologists and infectious disease specialists. Advances and new insights into the epidemiology, diagnosis, clinical manifestations and complications, treatment, and prevention of poxviral infections require a high level of expertise and interdisciplinary skills from healthcare professionals linking virology, infectious diseases, and dermatology. This CME article provides a systematic overview and update to assist the practicing dermatologist in the identification, differential diagnosis, and management of poxviral infections.

INTRODUCTION

"We have an outbreak that has spread around the world rapidly, through new modes of transmission, about which we understand too little […]",[1] said WHO Director-General T. A. Ghebreyesus when declaring the 2022/2023 mpox (monkeypox) outbreak in multiple non-endemic countries a Public Health Emergency of International Concern (PHEIC) in July 2022. It was the seventh PHEIC since the adoption of the International Health Regulations in 2005, but the first to be declared without consensus of the Emergency Committee.[1] This demonstrates that poxvirus infections continue to be an issue of concern, particularly for dermatologists and infectious disease specialists.

Molecular biology of poxviruses

Poxviruses are thought to have emerged about 500,000 years ago[2] and have been segregating and (co-)evolving ever since. They form a diverse family of complex and large, brick- or cocoon-shaped, enveloped double-stranded DNA viruses, comprising two subfamilies, i.e., *Chordopoxvirinae* infecting vertebrates and *Entomopoxvirinae* infecting insects. Chordopoxviruses currently include

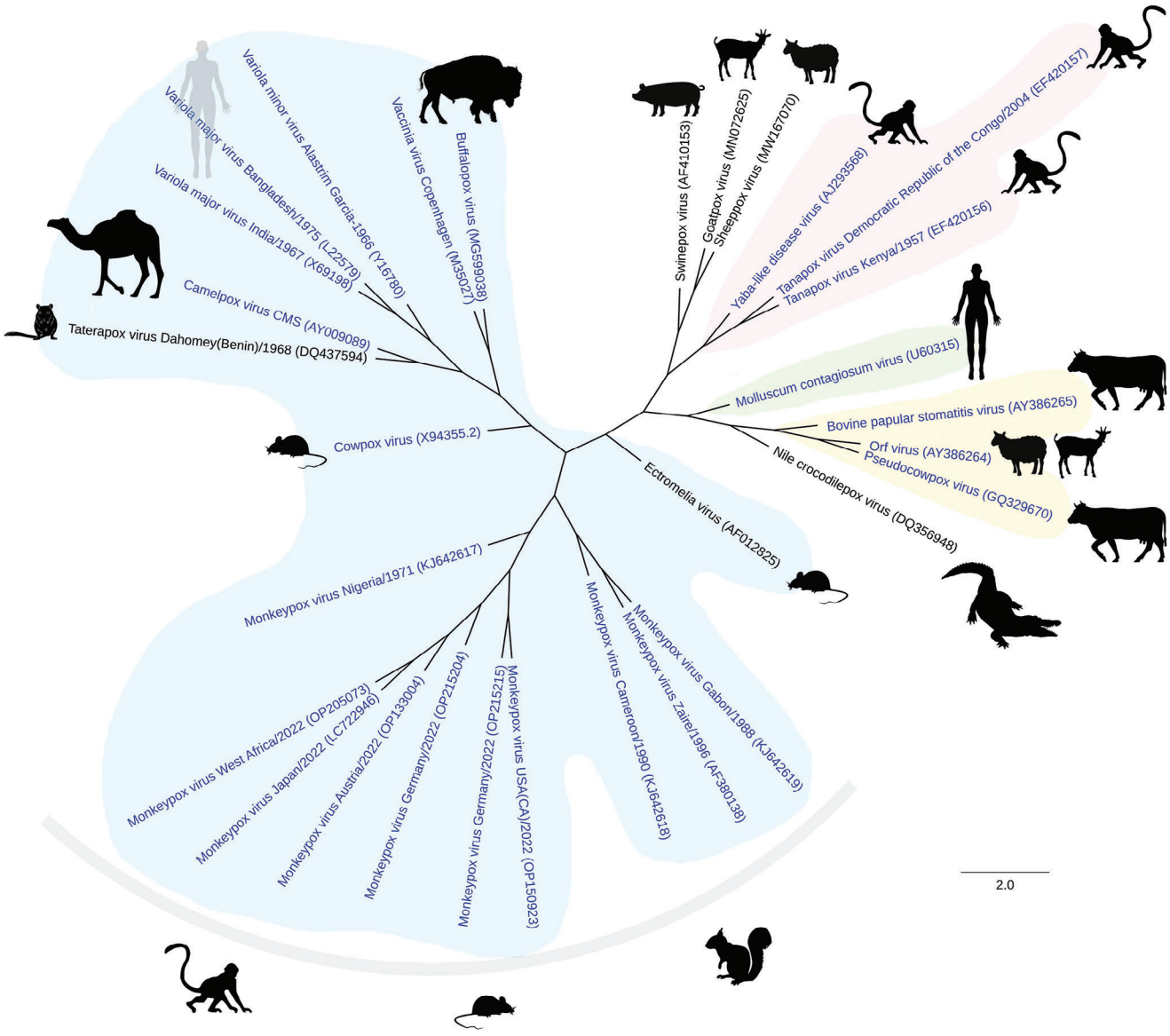

FIGURE 1 Phylogenetic tree[3] of poxviruses associated with human disease. Phylogeny was inferred from concatenated nucleotide sequences of the entire coding sequence of selected chordopoxviruses with full-genome sequences available on GenBank (accession numbers in brackets). Country and year of infection are indicated if available. The maximum-likelihood tree was obtained using RAxML 8.2.11[3] (GTR gamma model, 100 bootstrap replicates) implemented in Geneious prime 2022.2.2 and is shown in an unrooted format. The divergence scale reflecting substitutions per site is indicated. Pictograms show suspected natural hosts. Blue font color indicates known association with human disease. Background colors delineate the following poxvirus genera associated with human disease. Blue: *Orthopoxvirus*, green: *Molluscipoxvirus*, red: *Yatapoxvirus*, yellow: *Parapoxvirus*.

22 antigenically distinct genera. Human poxviral disease has been associated with members of four genera: *Ortho-*, *Para-*, *Mollusci-*, and *Yatapoxvirus* (Figure 1).[3]

Human poxviral disease has been associated with members of four genera: *Ortho-*, *Para-*, *Mollusci-*, and *Yatapoxvirus*.

Molluscum contagiosum virus and variola virus primarily infect humans, while other species have their natural reservoir in animals, causing zoonoses.

Molluscum contagiosum virus (MOCV) and variola virus (VARV) primarily infect humans (anthroponosis), while other species have their natural reservoir in animals, causing zoonoses.[4–6] Table 1 provides an overview of poxvirus genera and species, which have been associated with human infectious diseases.

Among all poxviruses, vaccinia virus (VACV) has been studied extensively and serves as the prototype of orthopoxviruses and related genera.[7] Research on VACV has revealed two major distinct infectious forms of poxvirus particles: *(1)* the highly resistant intracellular mature virion (MV) with a single membrane facilitating inter-individual transmission and *(2)* the more fragile extracellular enveloped virion (EV) with one additional outer membrane allowing for efficient intra-individual viral spread.[7,8] The fact that poxviruses have two such distinct

TABLE 1 Overview of poxvirus genera and species associated with human infectious disease.

Genus	Species	Associated human disease
Orthopoxvirus	*Buffalopox virus* (BPXV)*	Buffalopox
	Camelpox virus (CMLV)	Camelpox
	Cowpox virus (CPXV)	Cowpox (catpox)
	Mpox (monkeypox) virus (MPXV)	Mpox
	Vaccinia virus (VACV)	Vaccinia
	Variola virus (VARV)	Smallpox
Parapoxvirus	*Bovine papular stomatitis virus* (BPSV)	Papular stomatitis
	Orf virus (ORFV)	Orf
	Pseudocowpox virus (PCPV)	Milker's nodule (paravaccinia)
Molluscipoxvirus	*Molluscum contagiosum virus* (MOCV)	Molluscum contagiosum
Yatapoxvirus	*Tanapox virus* (TANV)	Tanapox
	Yaba-like disease virus (YLDV)*	Yaba-like disease

*May alternatively be considered a strain rather than a distinct species.

infectious forms is unique in the viral world, implicating not only environmental stability but extraordinary virus dynamics.[9] Poxviruses spread faster than their average replication time, e.g. VACV can infect one new cell every 1.2 hours on average but virion formation takes ≥ 5 hours. This is due to so-called superinfection repulsion, i.e. repulsion of EVs during intra-host spread by molecular flagging of the plasma membrane of already infected host cells, thereby accelerating conquest of yet uninfected cells up to fourfold.[10]

Poxvirus particles attach to host cell glycosaminoglycans and laminins. Highly conserved transmembrane proteins orchestrate fusion of the virion and host cell membranes. To date, no specific cell receptor has been identified that mediates fusion of the viral particle with the host cell.[7] Some poxviruses can infect a remarkable variety of species and even different classes of organisms. For example, prototypic VACV can infect diverse mammals, birds, and insects. Successful replication, however, depends on further intracellular virus-host-interactions. Following internalization of the virion, poxvirus replication takes place in the host cell cytoplasm. Of note, other double-stranded DNA viruses, including human papilloma- or herpesviruses require nuclear import for replication. Progeny poxvirus particles assemble in perinuclear factories starting approximately 2 hours *post* infection.[11] Cytosomal virus factories can be visualized by light microscopy as B-type inclusion bodies (Figure 2). B-type inclusion bodies in VACV- and VARV-infected cells are eponymously referred to as Guarnieri bodies.[12] Certain poxviruses, such as cowpox virus (CPXV), also produce eosinophilic proteinaceous matrices around viral particles

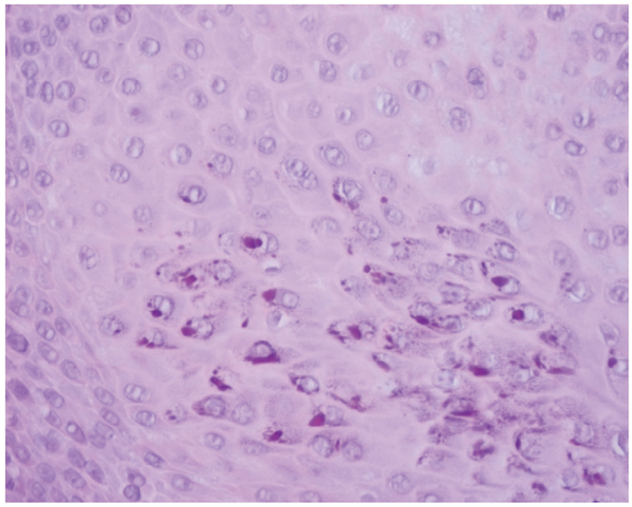

FIGURE 2 B-type inclusion bodies in mpox (monkeypox) virus (MPXV) infection (hematoxylin and eosin staining, original magnification x 40).

inside the host cell cytoplasm (A-type inclusion bodies), improving infectivity.[12,13]

Following internalization of the virion, poxvirus replication takes place in the host cell cytoplasm.

Poxviruses encode their own replication machinery and bring their own viral enzymes with them. Poxvirus DNA itself is not infectious.

Poxvirus progenies maturate and are released through cell lysis (MV) or budding if they have acquired an additional membrane from the Golgi apparatus (EV).[6,7,11,13]

Poxvirus interactions with the host

Large viruses are often equipped with a plethora of immune evasion strategies.[14] Poxvirus virions have an average size of 250 x 200 x 200 nm, almost equaling the size of bacterial *Mycoplasma genitalium*, for reference.[15,16] The poxviral genome encodes for approximately 200 proteins, > 50% of which are highly conserved across genera. The majority of conserved proteins contribute to viral replication while virus-host interactions can usually be attributed to less-conserved proteins.[7]

Intracellular virus-host interaction involves virotransducer and virostealth proteins.[17] Virotransducer proteins modulate innate immune reactions by inhibition of interferons, caspases, and repressing other apoptosis signals, e.g. oxidative burst.[14] To constitute an anti-oxidative intracellular milieu in the early stage of viral replication, the proteinaceous lateral bodies flanking each side of the core (Figure 3) are essential. Lateral bodies contain redox proteins impairing pattern recognition receptor-mediated signaling leading to autophagy and death of the infected host cell.[18]

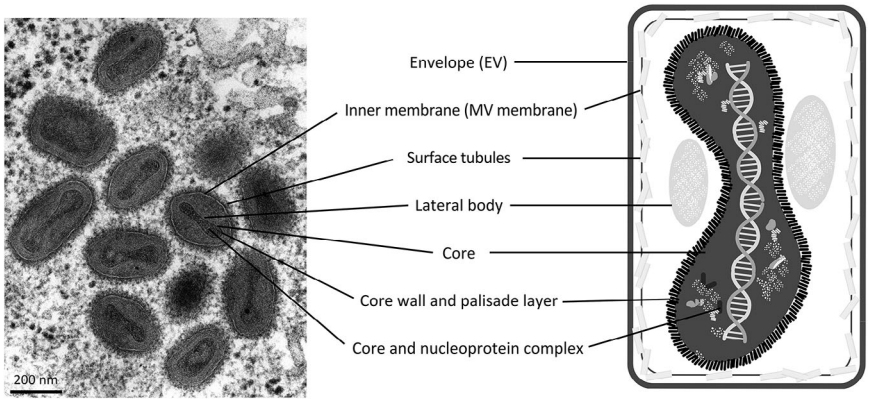

FIGURE 3 Overview of poxvirus morphology by the example of variola virus (VARV, orthopoxvirus). Transmission electron microscopy of VARV sampled from the last German smallpox case in Hannover, Germany in 1972 (source: Hans R. Gelderblom/RKI) and schematic illustration of the enveloped virion (EV)/ mature virion (MV).

Virostealth proteins hide signs of viral infection, thereby avoiding subsequent antiviral responses. Stealth strategies include subversion of DNA sensors, particularly those located in the host cell cytoplasm, such as gamma interferon inducible protein 16 (IFI16) or the absent in melanoma 2 (AIM2) protein. This disrupts inflammasome-mediated signaling, including interleukin (IL) 1β and IL-18 expression, induction of interferon-γ (IFNγ), and ultimately major histocompatibility complex (MHC) class I upregulation.[17,19–21]

Extracellular immunomodulation involves viromimic proteins, encompassing viroreceptors and virokines. Viroreceptors, such as tumor necrosis factor (TNF), IFN, or IL receptor homologs can bind specific cytokines and chemokines of the host. Virokines are viral homologs of their host counterparts, e.g. viral IL-10 of parapoxviruses which can suppress immune response.[22]

Natural killer cells, $CD4^+$ and $CD8^+$ lymphocytes, as part of the adaptive immune system, play a key role in viral clearance to control primary infection.[23,24] Only limited data is available on the risk of reinfection with a certain poxvirus species or strain, leading to symptomatic disease again. Evidence from the smallpox era suggests that generalized natural infection leads to life-long immunity. However, localized infection and vaccination, depending on the dose and route of administration, may induce limited immune protection.[25,26]

Poxvirus infection can severely impair quality of life, and there are increasing reports of complicated disease attributable to para/postinfectious processes as well as direct viral infection, including involvement of the central nervous system (CNS), respiratory tract, or connective and supportive tissues. Figure 4 provides an overview of the complications associated with natural poxvirus infection.[27–41]

Modes of transmission and disease progression

Anthroponotic or zoonotic poxvirus transmission can occur through different routes, mainly by direct contact, including fomites (contaminated items or surfaces) but also via the airborne route by droplets and virus-laden particles or presumably via arthropod vectors.[42,43] Poxviruses are considered hardy, especially under dry, cold, and dark conditions. But UV radiation and detergents can inactivate poxvirus particles efficiently.[44]

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Poxvirus DNA shedding has been demonstrated in a variety of samples, including semen, urine, feces, and saliva. However, the question whether these samples are infectious remains to be clarified on a case-by-case basis as poxvirus DNA itself is not infectious.[45] Poxvirus transmission via needle stick has been documented and transmission via blood products, i.e. transfusion, is considered possible but has never been reported.[46–48] In specific scenarios, e.g. the 2022/2023 mpox outbreak in non-endemic countries or in certain molluscum contagiosum cases, poxvirus infections are sexually transmittable infections (STI).[49,50]

Poxviral infection is generally considered contagious from the onset of symptoms until resolution of skin lesions.

Poxviral infection is generally considered contagious from the onset of symptoms until resolution of skin lesions (Table 2). However, mpox has been reported to be contagious during the pre-symptomatic stage already.[51]

Disease severity and manifestation, i.e. localized vs. generalized infection, may vary depending on multiple factors, including virus species, strain, route of transmission, infectious dose, and host factors, such as immunocompromisation.[52]

Poxviral infection of fibroblasts and keratinocytes in human skin usually remains localized. Especially MOCV cell tropism is exclusively restricted to basal epidermal keratinocytes.[53] Disruption of the skin barrier, e.g. a wound or microtrauma, is considered a *conditio sine qua non* for inoculation.[54]

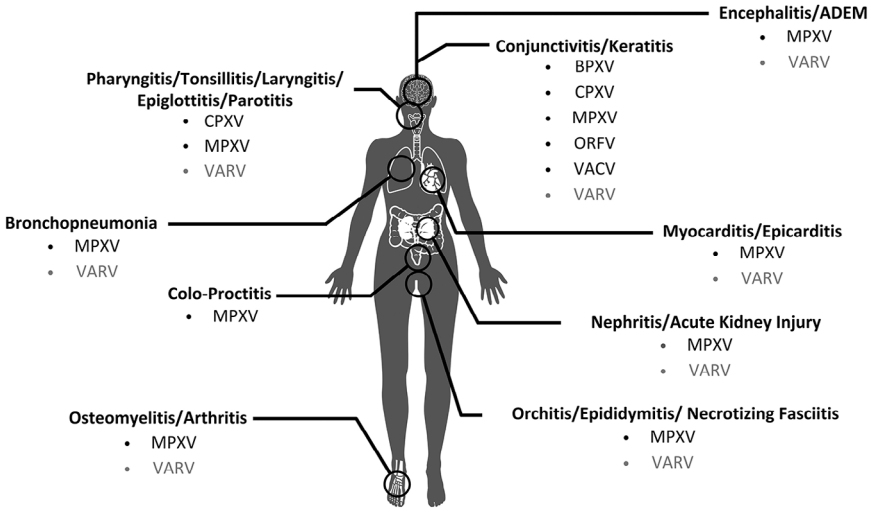

FIGURE 4 Overview of clinical manifestations/complications of natural poxvirus infection. *Abbr.*: ADEM, acute disseminated encephalomyelitis; BPXV, buffalopox virus; CPXV, cowpox virus; MPXV, mpox virus; ORFV, orf virus; VACV, vaccinia virus; VARV, variola virus (shaded in grey for official eradication of the virus).

TABLE 2 Overview of incubation periods after exposure and observed period of communicability of human poxvirus infections.

Disease	Incubation period	Period of communicability
Buffalopox	3–19 days	Exposure until crusts fall of (≈ 1-3 weeks)
Camelpox	3–19 days	–*
Cowpox (catpox)	7–12 days	–*
Milker's nodule (paravaccinia)	2–15 days	–*
Molluscum contagiosum	2–8 weeks	Duration of cutaneous lesions
Mpox	1–21 days	Exposure until crusts fall off (≈ 2–4 weeks)
Orf	3–7 days	Duration of cutaneous lesions
Papular stomatitis	2–5 days	–*
Smallpox	7–19 days	Exposure until crusts fall off (≈ 2–4 weeks)
Tanapox	3–5 days	–*
Vaccinia	≈ 5 days	Exposure until crusts fall off (≈ 1–3 weeks)
Yaba-like disease	3–5 days	–*

*No human-to-human transmission known.

Disruption of the skin barrier, e.g. a wound or microtrauma, is considered a *conditio sine qua non* for inoculation.

Poxviruses other than MOCV show broader tropism on the cellular and tissue levels.[53] Cells of the mononuclear phagocyte system are considered the primary targets of many poxviruses.[55,56] Upon contact with resident immune cells after entry into the skin, viral particles then migrate to peripheral lymph nodes. There, $CD169^+$ systemic macrophages, which are different from M1 and M2 macrophages, supposedly play a key role in preventing viremia, i.e. dissemination.[55,56] Some poxviruses however, e.g. VARV and MPXV, can silence such systemic macrophages in secondary lymphatic organs, thus evading viral clearance at this stage.[57]

Generalized infection occurs when viral particles migrate into draining lymph node(s), then causing leukocyte-associated viremia, i.e., hematolymphatic spread. During a first viremic phase, patients usually experience prodromal symptoms, e.g., malaise, fever, or lymphadenopathy. Viremia allows for further hematogenous seeding to other organs and the entire integument.[15,55,58] Of note, viremia may not occur with all poxvirus infections: while VARV, MPXV, or CPXV DNA has repeatedly been detected in blood samples (as a surrogate parameter of viremia), MOCV DNA has rarely been detected in blood,[59] for example.

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Detection methods

- Real-time polymerase chain reaction (RT-PCR) has become a widely used detection method.[60,61] Suitable sample types include swabs or aspirates from skin lesions, "touch preps", throat swabs/saliva, ocular swabs, and/or scabs, depending on individual clinical presentation. Samples may be collected dry or in universal/viral transport medium, refrigerated, frozen or at room temperature, and referred to a biosafety level 2 laboratory facility as soon as possible.[62] Other sample types may include urine, feces, semen, or EDTA blood, particularly in research settings for diagnostic issues concerning reliability of results.[45,62] Formalin-fixed, paraffin-embedded (FFPE) tissue samples can be used for PCR testing but cross-linking and fragmentation of DNA may negatively impact diagnostic accuracy and interpretation of viral loads.[63]
- Electron microscopy has long been used to detect and differentiate the large brick- or cocoon-shaped virions of

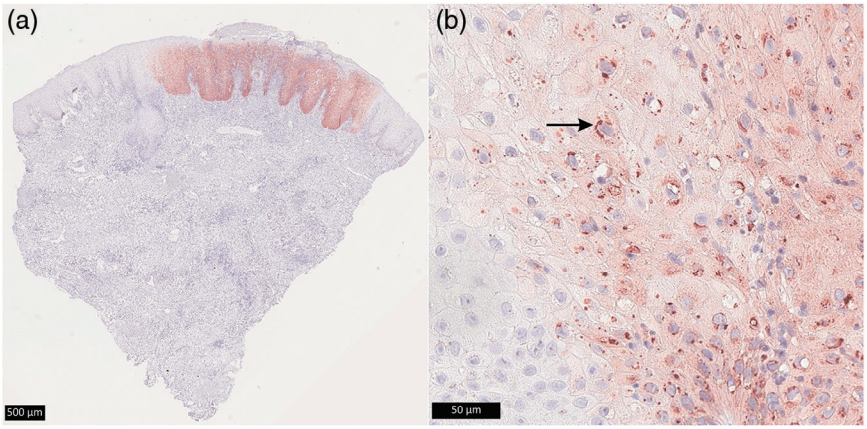

FIGURE 5 Immunohistochemical staining of a perianal skin lesion for the detection of orthopoxviruses, specifically MPXV (FFPE). Orthopoxvirus generic immunohistochemical staining using anti-CPXV antibodies with positivity in the cytoplasm of infected keratinocytes of the lesional epidermis. Clear demarcation from the non-infected perilesional epidermis: (a) overview (original magnification x 40) and (b) detailed view of cytoplasmic and markedly perinuclear (arrow) but not nuclear staining (original magnification x 100), used by courtesy of A. Breithaupt, DVM.

poxviruses from other virus families. Among preferred sample types for electron microscopy are aspirate samples from vesicles or pustules. These can be collected using a 26–29 gauge needle or a capillary tube after sterile lancing of a skin lesion. Alternatively, a direct smear can be collected on a glass slide (touch prep). Swabbing is not suitable for electron microscopy. Electron microscopy, which is considered a fast and unbiased detection method, is usually performed in facilities with designated expertise only.[5,64]

- Second-line diagnostics include viral cultures and agnostic metagenomics, which has been performed to detect the first Brazilian case of mpox in 2022, for example.[62,65] Beyond detection, next-generation sequencing (NGS), including recent developments such as long-read sequencing (e.g. nanopore sequencing), can enable whole-genome sequencing within reasonable time. These advanced technologies hold the promise of timely detection and tracking of outbreaks. Also, they open up the possibility of detecting even small mutational details such as single nucleotide polymorphisms (SNPs) across the full length of the genome and, ultimately, uncovering evolutionary trends with potential clinical relevance.[66]
- Serological testing alone is not recommended for confirmation of acute poxvirus infection but can help to rule-out an acute infection. Detection of poxvirus species-specific antibodies from the blood (serum or plasma) is not conclusive, as orthopoxviruses trigger similar immune responses (cross-reactivity).[62]

The mainstay of poxvirus diagnostics is laboratory testing upon reasonable suspicion based on patient signs and symptoms and/or patient history.

Real-time polymerase chain reaction (RT-PCR) has become a widely used detection method.

Histopathological examination, including immunohistochemistry (Figure 5) can be a valuable adjunct to molecular virology detection methods. Early dermatohistological findings in the maculopapular stage include dilatation of small capillaries and lymphatics, epidermal hyperplasia, and ballooning of keratinocytes reflecting cytopathic effect. Later during the vesicular stage, acanthosis, spongiosis, and edema of the *stratum basale*, basal membrane, and dermal *papillae* can be seen. Perivascular and interstitial mixed infiltrates of lymphocytes and plasma cells, eosinophils, and neutrophils, partially with fragmentation of nuclei, i.e., nuclear dust (leucocytoclasia) are common. During the vesicular stage, there may be further ballooning degeneration of keratinocytes with only few viable keratinocytes left. Remnant viable keratinocytes may display multiple eosinophilic nucleoli, reminding of intranuclear inclusion bodies, starting in the papular stage.[67–69] Cytoplasmic B-type inclusion bodies (Figure 2) staining reddish-purple with Giemsa or hematoxylinophilic with hematoxylin stain close to the nucleus representing viral factories are considered a characteristic microscopic feature of all human poxviral infections.[12,13,68] The term 'Guarnieri body' should exclusively be used for VACV and VARV B-type inclusion bodies to circumvent past historical inaccuracy in the use of the designation.[12] Eosinophilic A-type inclusion bodies (Feulgen-negative) can be seen in CPXV infection.[12,70] During the pustular stage, large numbers of neutrophils can be found in the dermis which migrate into the epidermis and form a pustule. In the stage of umbilication and ulceration, necroses develop which reach into the deep dermis resulting in scar formation.[30]

An overview of diagnostic facilities providing different detection methods in EU (candidate) countries can be obtained from the Emerging Viral Diseases-Expert Laboratory Network (EVD-LabNet) online directory search.[71]

ORTHOPOXVIRUS INFECTIONS

Smallpox – A short historical discourse

Smallpox was one of the most feared viral infectious diseases of all time, caused by the highly contagious VARV of the genus *Orthopoxvirus*. VARV has presumably emerged

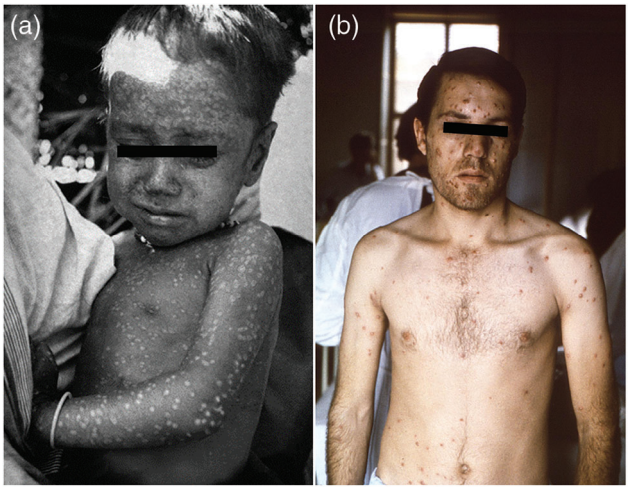

FIGURE 6 Last known case of naturally-occurring smallpox and centrifugal distribution pattern of ordinary smallpox. (a) Historical photograph from 1975, showing 2-year-old Rahima Banu from Kuralia, on Bhola Island, in the district of Barisal, Bangladesh, who was the last known case of naturally-occurring smallpox worldwide (used by courtesy of the US Centers for Disease Control and Prevention and the World Health Organization, Stanley O. Foster MD, MPH, image deposited at the Public Health Image Library) and (b) typical centrifugal distribution of ordinary smallpox with vesiculopustular exanthem on the extremities and face. Historical photograph from 1968 (used by courtesy of the US Centers for Disease Control and Prevention, Dr John Noble, Jr. deposited in the Public Health Image Library).

in Africa, 3,000–4,000 years ago and adapted to humans as the only natural reservoir.[72] The first references to smallpox are thought to be in Indian scriptures from as far back as 1500 BC. Within the 20th century, smallpox caused an estimated 500,000 deaths until its worldwide eradication as a result of an intensified global surveillance and vaccination campaign organized by WHO from 1967 to 1979/1980.[73] The last known case of naturally-occurring smallpox was reported from Bangladesh in 1975 (Figure 6a), and since then VARV has only been known to exist in two protected locations, the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, USA and the State Research Center of Virology and Biotechnology (VECTOR Institute) in Koltsovo, Russia.[73–75]

Two primary clades of VARV can be classified for differences in molecular virology and clinical presentation: Variola major and Variola alastrim minor, the first of which accounting for severe and fatal disease in approximately 30% of cases, especially among unvaccinated individuals.[30,72,76] According to a WHO classification, there were five forms of smallpox: ordinary, modified, variola *sine eruptione*, flat, and hemorrhagic. Ordinary smallpox, the most common form, led to a vesiculopustular discrete, (semi-)confluent rash primarily affecting the face and extremities (Figure 6b). The incubation period was 10–14 days and systemic symptoms, usually during the pre-eruptive stage, included fever, head-, and backache. Modified and variola *sine eruptione* were usually mild. Flat and hemorrhagic smallpox however, were associated with mortality rates of almost 100%.[30]

Smallpox no longer poses an immediate threat but remains one of the "dirty dozen" of pathogens with bioterrorist potential.[77]

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Mpox (monkeypox)

On August 22, 1970, a 9-month-old boy became ill with a fever and subsequent rash in a tropical rainforest village near Bokenda, Mongala, Democratic Republic of the Congo. The patient deteriorated with otitis and mastoiditis and was referred to a municipal hospital where samples were taken to confirm the suspicion of smallpox. Those samples tested negative for VARV but positive for MPXV at the WHO Collaborating Center on Smallpox and Other Related Infections at the then Moscow Research Institute for Viral Preparations.[78] This was the first documented case of human monkeypox. The boy who made history recovered from monkeypox but died from measles few weeks later.[78]

Ever since, sporadic cases and smaller outbreaks were reported from Sub-Saharan countries where the disease is considered endemic: Sierra Leone, Liberia, Côte d'Ivoire, Nigeria, Benin, Cameroon, Central African Republic, South Sudan, Gabon, Republic of the Congo, and Democratic Republic of the Congo, the latter of which forming the epidemiological epicenter.[55,79,80]

In 2003, monkeypox aroused attention when the first outbreak in non-endemic countries was detected in multiple midwestern US states. The most likely source of infection were MPXV-infected pet prairie dogs housed with ill Gambian pouched giant rats. No human-to-human transmission was observed during this outbreak.[81–83]

From 2003 to 2018, case reports were confined to endemic countries. Between 2018 and 2021 however, multiple smaller outbreaks were detected in the Western hemisphere, including a first case of inter-human transmission.[84–87]

The largest outbreak involving multiple non-endemic countries is considered to have started in May 2022 and was declared a PHEIC in July 2022. The majority of cases in this PHEIC were detected in the US, followed by Brazil, Spain and other western European countries, including Germany (Figure 7).[88] During 2023, the number of laboratory-confirmed mpox cases in non-endemic countries declined, and the PHEIC was officially declared over by WHO in May 2023.[89,90] More than 80,000 cases were reported worldwide during this period. However, cases of mpox continued to be reported in several WHO regions in 2023,[91–94] suggesting that the endemic risk has spread beyond the original endemic areas. This outbreak constituted a prime example of evolution chang-

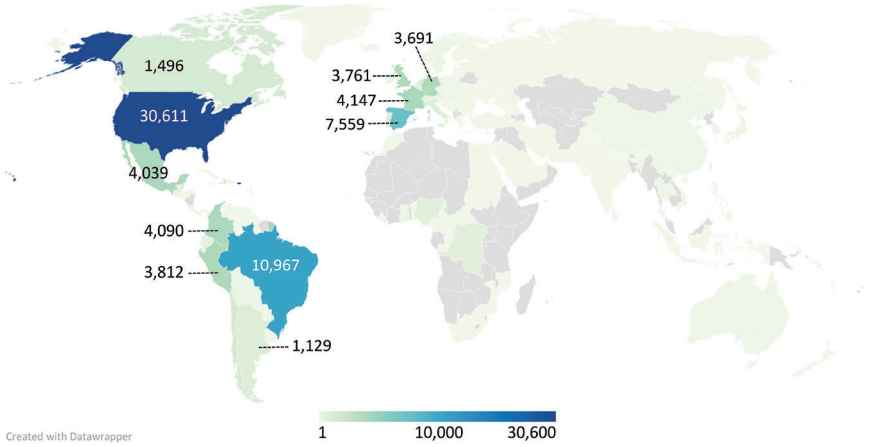

FIGURE 7 Global mpox case counts in the 2022/2023 outbreak in previously non-endemic countries between January 01, 2022, and June 19, 2023. Case numbers ≥ 1000 per state/federation of states are shown in detail (created with datawrapper: https://datawrapper.dwcdn.net/eT5ba/1/).

Nomenclature

On November 28, 2022, WHO announced their recommendation to change the English term "monkeypox" to "mpox" to avoid stigmatization. For a transitional period of one year, both terms ("mpox"/"monkeypox") will be used and then completely replaced by "mpox". However, "monkeypox" will remain searchable in the International Classification of Diseases (ICD) in the future.

ing an infectious disease's epidemiological and clinical characteristics.

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Pathogen and transmission

Monkeypox, now called "mpox" as a synonym and the new preferred term,[95] was considered a rare tropical zoonosis. Most likely, rodents and/or small mammals, including non-human primates in rainforest regions are the natural host and reservoir of MPXV.[55,96] In endemic countries, MPXV spillover infection has been associated with close contact, hunting, or consumption of wildlife.[55,78,97] Biogeographical borders between the Central African Congo Basin and Western Africa may have influenced the segregation and co-evolution of distinct phylogenetic clades:[96] clade I (Central African) and II (West African) with subclades IIa and IIb, as of 2023 (Figure 8).[98]

Our phylogenetic analysis based on publicly available MPXV genome sequences from 40 different countries from 1970–2023 shows that representatives of all clades are currently circulating. While genome sequences from clades I and IIa are predominantly from the WHO African region, clade IIb is more diverse, with countries of origin from all WHO regions (Figure 8). To account for genetic and epidemiological differences, the clade IIb subgroup has been named human MPXV (hMPXV).[98] Whole-genome analyses have shown that hMPXV has a surprisingly high mutation rate of about twelve mutations per genome per year. These and other evolutionary changes within the clade (or beyond) could potentially prove clinically relevant.[66]

During the 2022/2023 mpox outbreak, human-to-human transmission has been considered a characteristic feature, mainly involving close, intimate, and sexual contact between men who have sex with men.

In the recent epidemiological context, MPXV/hMPXV infection is considered an STI.

During the 2022/2023 mpox outbreak, human-to-human transmission has been considered a characteristic feature, mainly involving close, intimate, and sexual contact between men who have sex with men (MSM/GBMSM).[29,99] In the recent epidemiological context, MPXV/hMPXV infection is considered an STI.

Alternative routes of transmission include short-distance airborne transmission, vertical transmission from mother to child, needle stick injury, or via indirect contact with infected particles.[46,55,102] Transmission can occur via fomites and surfaces, such as textile fabrics (e.g. towels), cutlery and dishes, mobile phones, or doorhandles.[103] Viable MPXV particles have been detected on surfaces for up to 15 days.[104]

For infected individuals, local regulations may apply regarding infection control measures, such as isolation and specific disinfection procedures, as well as containment of potentially infectious items, e.g. bandages and toiletries.[44,105] As long as symptoms persist, usually until crusts fall off within 2–4 weeks, transmission is possible. Strict precautions are advisable if the clinical picture is severe and there are, for example, skin lesions on areas not covered by clothing, especially on the face and hands, which increases the probability of non-sexual transmission. Contacts with vulnerable individuals should be avoided.[101,105,106] Viable MPXV has also been detected in

FIGURE 8 MPXV phylogenetic analysis[3]. Phylogeny was inferred from the core genome nucleotide sequence (position ≈ 60,000–170,000) of 117 selected MPXV genomes dating from 1970-2023 from 40 different countries with full-genome sequences available on GenBank (accession numbers in brackets). Country and year of infection are indicated if available. Nucleotide sequences were aligned using MAFFT[308] (Multiple Alignment using Fast Fourier Transform) v7.490 (default parameters); 5′ inverted terminal repeat (ITR) sequences were trimmed. The maximum-likelihood tree was obtained using RAxML 8.2.11[3] (GTR gamma model, 100 bootstrap replicates) implemented in Geneious prime 2023.2.1 and is shown in an unrooted format. The divergence scale reflecting substitutions per site is indicated. Orange font color indicates clade I, green for clade IIa, brown for clade IIb-A and turquoise for clade IIb-B (hMPXV).

seminal fluid.[107] Therefore, people who have had mpox should continue to use a condom during sex for 8 weeks after all lesions have healed.[101,105]

National health authorities provide detailed recommendations on the management of close mpox contacts. The most important measures are self-monitoring and seeking medical attention in case of symptoms, as well as post-exposure prophylaxis (PEP).[105,106,108]

Mpox as a zoonotic infection has gained new momentum with the first detection of potential human-to-dog transmission of MPXV/hMPXV.[109,110] To prevent spillover and/or spillback, close contact to animals should be avoided in the infective stages of mpox.

Clinical presentation

The average incubation period of mpox is 9–13 days, mainly depending on the type of exposure, i.e., shorter intervals for invasive and/or complex (e.g. through wounds

or mucosal exposure) vs. longer intervals for non-invasive exposure (e.g. by droplets via the respiratory route). The extremes of the incubation period range from 1–21 days.[111–113]

MPXV infection can be divided into two stages: the invasion or pre-eruptive period (first viremia) where patients might experience fever, headache, malaise, and/or lymphadenopathy and the eruptive period (following secondary viremia) where skin lesions evolve.

MPXV infection can be divided into two stages: the invasion or pre-eruptive period (first viremia) where patients might experience fever, headache, malaise, and/or lymphadenopathy and the eruptive period (following secondary viremia) where skin lesions evolve.[27]

Clinical picture in endemic countries (prior to 2022): During the pre-eruptive period, submandibular and cervical lymphadenopathy during the first 3 days following fever, sometimes progressing to disseminated lymphadenopathy later in the course of illness were among the most typical symptoms of mpox. The eruptive period was classically characterized by skin lesion appearing in a centrifugal pattern and including palms and soles, but less severely affecting the trunk. Skin lesions would usually follow a monomorphic sequence of sometimes painful or itchy macules to papules, oftentimes with central umbilication, over vesicles to pustules which would ultimately develop a crust and fall off. Lesions often heal with scarring.[27]

Clinical picture in previously non-endemic countries (since 2022): In the 2022/2023 mpox outbreak, the median incubation period of 8–9 days[114] was observed to be shorter than for non-primarily sexual, and thus less invasive/complex, modes of transmission in originally endemic countries prior to 2022 (8–13 days). In Germany, data analysis of 161 cases with defined exposure time during the 2022 outbreak showed a shortened incubation period of 1–3 days.[113]

Likewise, the clinical presentation of mpox of the 2022/2023 outbreak was distinct from previous endemic outbreaks considering the typical location of lymphadenopathy and skin lesions as well as the temporal sequence of efflorescences. Patients acquiring mpox as an STI may more frequently experience inguinal[115,116] and/or anal lymphadenopathy, the latter of which might be underestimated for diagnostic difficulty. Mpox patients now often experience asynchronous development of skin eruptions.[55,115,117] Skin eruptions may exclusively occur in the anal, genital, or anogenital region or in the oral cavity and/or anal canal, potentially correlating with the location of primary inoculation.[115] Newly reported clinical features of mpox include tenesmus, defecation pain, purulent or bloody stools, and/or penile edema (Figure 9) as well as Fournier's gangrene-like complication.[118]

Likewise, the clinical presentation of mpox of the 2022/2023 outbreak was distinct from previous endemic outbreaks considering the typical location of lymphadenopathy and skin lesions as well as the temporal sequence of efflorescences.

During the 2022/2023 outbreak in non-endemic countries, atypical mpox and associated complications affecting other organ systems than the skin (Figure 4) were reported, e.g. ophthalmic manifestations,[119] arthritis and osteomyelitis,[36] myocarditis,[37] or encephalitis/encephalomyelitis.[28,39] Secondary complications include bacterial superinfection.[27,55,118,120]

Overall, mpox can be asymptomatic or subtle, self-limiting disease (2–4 weeks)[55,121] or progress to fatal outcome.[27,55,122,123] Disease severity has been shown to be clade-dependent, viz. clade I has been associated with higher case fatality rates ranging from 0–11%[124] compared to < 4% for clade II.[80] The 2022/2023 global outbreak was traced back to clade II (Figure 8).

Diagnosis

Patients should be interviewed about the sequence of signs and symptoms (including prodromal symptoms during the pre-eruptive period), travel history and festival gathering, sexual behavior (GBMSM, non-exclusive partnership, condom use, etc.), occupation (sex workers, health care workers, zookeepers, etc.), risk contacts, animal contact, underlying medical conditions (especially immunocompromising conditions), and vaccination status.[99,115,125] Health care experts should always account for the risk of stigma, discrimination, and increasing homophobia.[126]

To standardize mpox diagnoses, consensus case definitions have been endorsed by public health authorities, including the US and European Centers for Disease Control and Prevention (Table 3).[106]

RT-PCR can usually detect all MPXV clades with very high accuracy. In some laboratories, dual testing for MPXV and orthopoxviruses is performed to increase diagnostic sensitivity.[127]

Electron microcopy, histopathology findings, and immunohistochemistry (Figures 2, 5) can help to make an mpox diagnosis. However, histopathological differentiation of mpox from other viral infections can be challenging and electron microscopy may only be available at specialized institutions.

Recent developments in the diagnosis of mpox include artificial intelligence and machine learning methodologies. In particular, deep neural networks, multi-layered mathematical models, promise to be a reliable decision-making tool in differentiating mpox from chickenpox or measles based on the morphology and location of lesions.[128]

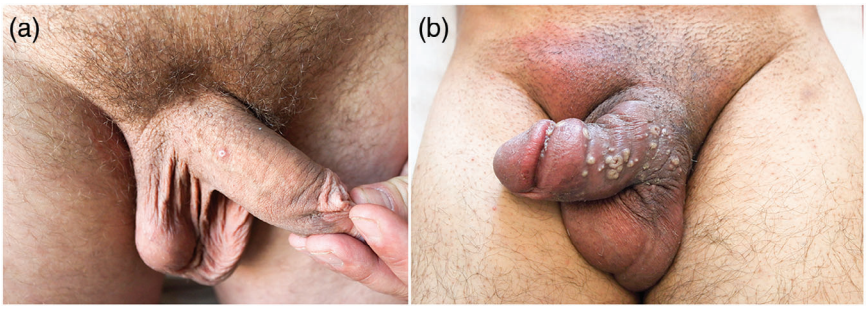

FIGURE 9 Clinical spectrum of penile mpox after sexual transmission (STI). (a) 34-year old patient presenting with a solitary penile umbilicated pustule (3–4 mm diameter) and most discreet surrounding reaction, MPXV-positive by PCR and (b) 59-year old patient presenting with > 40 penile and scrotal pustules, partly umbilicated and/or confluent, extensive penile edema and inguinal lymphadenopathy (bubo), MPXV-positive by PCR.

TABLE 3 Mpox case definition, adapted from the CDC case definition for use in the 2022 mpox response.[106]

Suspected Case	Probable Case	Confirmed Case
New characteristic rash OR Meets one of the epidemiologic criteria* and has a high clinical suspicion for mpox	No suspicion of other recent orthopoxvirus exposure AND Demonstration of the presence of orthopoxvirus DNA by PCR OR Demonstration of the presence of orthopoxviruses using immunohistochemical or electron microscopy testing methods OR Demonstration of detectable levels of anti-orthopoxvirus IgM antibody during the period of 4–56 days after rash onset	Demonstration of the presence of MPXV DNA by PCR or next-generation sequencing of a clinical specimen OR Isolation of MPXV in culture from a clinical specimen
Epidemiologic Criteria, within 21 days of illness onset: Reports having contact with a person/people with a similar appearing rash or who received a diagnosis of confirmed or probable mpox OR Had close or intimate in-person contact with individuals in a social network experiencing mpox activity, this includes GBMSM who meet partners through an online website, app, or social event OR Traveled abroad to a country with confirmed cases of mpox or where MPXV is endemic OR Had contact with a dead or live wild animal or exotic pet that is an African endemic species or used a product derived from such animals (e.g., game meat, creams, lotions, powders, etc.)		
Exclusion Criteria An alternative diagnosis can fully explain the illness OR An individual with symptoms consistent with mpox does not develop a rash within 5 days of illness onset OR A case where high-quality specimens do not demonstrate the presence of orthopoxviruses or MPXV or antibodies to orthopoxviruses		

Abbr.: GBMSM, gay, bisexual, and other men who have sex with men; DNA, Deoxyribonucleic acid; MPXV, mpox virus; PCR, polymerase chain reaction

STI diagnostics

For frequently reported STI co-infection(s), including HIV and hepatitis B and C virus infection, gonorrhea, *Chlamydia trachomatis* infection, *Mycoplasma genitalium* infection, and syphilis,[29] we recommend to test for STI as a key component of the diagnostic work-up in the context of sexually transmitted mpox.

Mandatory reporting

Many countries have legislated mandatory reporting of suspected cases and/or confirmed mpox diagnoses to public health authorities and compliance with infection prevention and control recommendations. In Germany, notification is required in accordance with § 6 Section 1 No. 5 IfSG for clinicians and § 7.2 IfSG for laboratories.

However, the practical use of such technical developments remains to be discussed, and the importance of virological testing will remain undisputed for the time being.

Prevention and therapy

Primary prevention strategies include avoiding risk contacts, mainly sexual/intimate contact with people showing

signs and symptoms of mpox or who have an epidemiological link to mpox but also avoiding contact with surfaces that were used by mpox patients and/or potentially infected animals. Hygiene measures using alcohol-based disinfectant and/or soap help reduce the risk of transmission.

WHO endorses primary preventive vaccination against mpox for risk groups, such as GBMSM, sex workers, transgender people, healthcare and laboratory personnel using second- or third-generation smallpox vaccines, inducing cross-protection against MPXV.

The indication for vaccination of other individuals, e.g. (iatrogenically) immunocompromised individuals, must be evaluated on a case-by-case basis.[129]

Individuals who have been vaccinated against smallpox up until 1980, when smallpox where officially declared eradicated and mass vaccination programs for the general population were stopped, are thought to be protected against severe manifestation of mpox for several decades.[130] However, breakthrough infections have recently been observed in this group of people, so booster shot(s) may be useful.[131]

Initially, first-generation vaccines such as Dryvax (US) or Lister/Elstree (UK) containing live VACV propagated on the skin of live animals were used but are no longer available because they do not meet modern standards of good manufacturing practice (GMP) and have been associated with severe adverse events following immunization (AEFI). As of 2022, two vaccines are approved by the U.S. Food and Drug Administration (FDA): the second-generation live and replication-competent cell culture-derived VACV vaccine ACAM2000 and the third-generation live attenuated Modified Vaccinia Ankara (MVA) vaccine, branded Jynneos/Imvamune/Imvanex.[132,133] Another second-generation vaccine, the Aventis Pasteur Smallpox Vaccine (APSV) is available as an investigational vaccine for emergency use.[133] In the EU, only third-generation Imvanex has been authorized for smallpox, vaccinia, and mpox vaccination as of 2022.[134] Data from 2023 show that third-generation vaccines are 68.1% effective at preventing MPXV infection after one dose and 88.5% effective after the second dose.[135]

Japan has licensed third-generation LC16m8 vaccine in 1975.[136] Table 4 provides an overview of approved smallpox/mpox vaccines.[108,133,137]

Post-exposure prophylaxis is recommended by WHO following high- or medium-risk exposure using any of the vaccines approved, ideally within 4 days or up to 14 days if the individual at risk has not yet developed any signs and symptoms of mpox. High-risk exposure is defined as direct contact to MPXV-infected skin, secretions, excretions, or surfaces without personal protective equipment. Medium-risk exposure is considered any closer but not direct contact with infectious materials without wearing personal protective equipment. Mpox PEP is considered efficacious and well-tolerated but data are limited.[138] Preliminary results from a 2022 observational study showed, that 4% of PEP recipients (n = 276) experienced breakthrough infection following administration of a third-generation vaccine.[139]

Post-exposure prophylaxis is recommended by WHO following high- or medium-risk exposure using any of the vaccines approved, ideally within 4 days or up to 14 days if the individual at risk has not yet developed any signs and symptoms of mpox.

Anyone exposed who has had primary preventive vaccination is not recommended to receive PEP.[137]

Therapeutic options for mpox include symptomatic treatment, e.g., pain killers or local anesthetics. Local antiseptics may be used, e.g., chlorhexidine gluconate mouthwash, or antimicrobial therapy, e.g., antibiotic eyedrops, depending on the localization of lesions and (impending) complications, such as bacterial superinfection. Hospitalization is not necessary or useful *per se*.

No antiviral treatment has been approved for MPXV infections until 2023. Off-label treatment options include intravenous cidofovir and its lipid ester oral brincidofovir as well as oral/intravenous tecovirimat. The latter has been authorized for mpox under "exceptional circumstances" upon written request to health authorities in the EU. Both, cidofovir and brincidofovir are DNA polymerase inhibitors with antiviral activity against various DNA viruses, e.g., human adenoviruses or cytomegalovirus. The level of clinical experience may be greatest for the use of cidofovir, but concerns about renal toxicity often remain a hurdle to its broader use. Brincidofovir may have better tolerability and a wider safety margin, but may not be readily available in both, the EU and US. Tecovirimat inhibits the enveloping of orthopoxvirus particles, i.e., formation of EVs thus disturbing intra-host transmission between cells. Tecovirimat is approved for use against smallpox in Canada, the EU, and US but may have similar efficacy against other orthopoxviruses, including MPXV. Tecovirimat is well tolerated and can shorten the duration of viral shedding. A mutation in the orthopoxvirus genome at a single position in the amino acid sequence can cause resistance to tecovirimat, so the indication for administration should be strict.[140,141]

Vaccinia immune globulin (VIG) made from pooled plasma of smallpox vaccinees for intravenous or intramuscular administration is also among treatment options for complicated mpox but its efficacy remains unclear and it may not be commercially available.[142]

For ocular mpox, trifluridine eye drops have been used off-label to prevent secondary complication and blindness.[119] Trifluridine is a well-tried thymidine analog inhibiting viral DNA polymerase activity, used against herpetic keratitis but also smallpox keratitis in the past and including smallpox vaccination/ vaccinia keratitis.[143]

Supportive use of topical steroids may be considered on a case-by-case basis to relieve local inflammation.[143]

TABLE 4 Overview of approved smallpox/mpox vaccines as of 2023.

Vaccine	Generation/ Vaccine type	Schedule	Indication	Immune reaction	Protection
ACAM2000	2nd generation, replication-competent vaccinia virus	1 dose, percutaneous, multiple puncture technique, e.g. using bifurcated needle ≈ 15 x; booster dose every 3 years	People aged ≥ 1 year at risk of contracting MPXV; not recommended during pregnancy or for immunocompromised individuals; approved in multiple countries except EU	Red, itchy sore spot → blister → scab → scar ("take"); AEFI may include myopericarditis/pericarditis and vaccinia virus transmission	Peak immunity 4 weeks post vaccination; correlate of protection not established; long-term protection is unknown
Jynneos/ Imvamune/ Imvanex	3rd generation, replication-deficient Modified Vaccinia Ankara (MVA)-derived	2 doses ≥ 28 days apart, subcutaneous or intradermal (off-label as of 2022); only 1 dose if previously vaccinated against smallpox	Adults at risk of contracting MPXV; may be used during pregnancy or for immunocompromised individuals, including in atopic dermatitis patients; approved in EU, Canada, US	Myalgia, fatigue, rash, erythema, pain, swelling, or itching at the inoculation site; no serious AEFI have been reported	Non-inferior to ACAM2000 after 42 days when 2nd dose was given after 28 days; correlate of protection not established; long-term protection is unknown
LC16-Kaketsuken	3rd generation, minimally-replicating vaccinia virus	1 dose, percutaneous, multiple puncture technique, e.g. using bifurcated needle 5–10 x	People of all ages at risk of contracting MPXV; may be used during pregnancy or for immunocompromised individuals, including in atopic dermatitis patients (off-label as of 2022); approved in Japan	Lymphadenopathy, fever, fatigue, rash, erythema at the inoculation site, joint pain, swelling at the inoculation site; no serious AEFI have been reported	Non-inferior to Dryvax; correlate of protection not established; long-term protection is unknown

Abbr.: AEFI, adverse event following immunization; EU, European Union; US, United States (of America); MPXV, mpox virus

Exemplary clinical vignette

In June 2022, a patient presented to a tertiary care hospital, exemplifying the typical patient risk group and history, clinical signs and symptoms, and potential complications of mpox as an STI:

A Hispanic male HIV-positive patient of about 30 years on antiretroviral therapy (HIV-1 RNA < 20 copies/ml, lymphocyte counts within normal limits) noticed fatigue, sore throat, and fever (t_{max} 38 °C/100.4 °F) for 1 week before he developed cervical lymphadenopathy as well as disseminated pustules and papules, including painful umbilicated perianal papules. The patient reported unprotected receptive anal intercourse with a previously unknown male partner, casually arranged via dating app in Germany few days prior to the onset of pre-eruptive symptoms. The patient did not report any recent festival gatherings, sex work, or contact to animals. He reported a 7-day trip to another Central European country 4 weeks before the onset of symptoms. The patient did not know of any past STIs except for controlled HIV infection. He reported vaccination against hepatitis B but nothing else.

A swab from a perianal lesion tested MPXV-positive by PCR (cycle threshold value 22.06, reflecting high viral load). Next-generation sequencing revealed close relationship to other outbreak-related sequences of clade IIb/hMPXV (GenBank accession number: OP326284). Histopathology showed epidermal ulceration, extensive necrosis, and an incipient nodular confluent, diffuse dermatitis during the papular stage (Figure 10c); the lesional epidermis tested positive for orthopoxviruses by immunohistochemical staining (Figure 5). STI diagnostics revealed resolved hepatitis C and syphilis, which had been unknown to the patient. The patient went into isolation for 21 days in accordance with local infection control regulations and treated his lesions with zinc suspension. At follow-up after isolation, the patient tested MPXV-negative. He reported perianal scarring and extremely large effect on quality of life as reflected by the Dermatology Life Quality Index (DLQI) scoring 21/30. Figure 10 displays the distribution of lesions, a clinical picture, and histopathology findings.

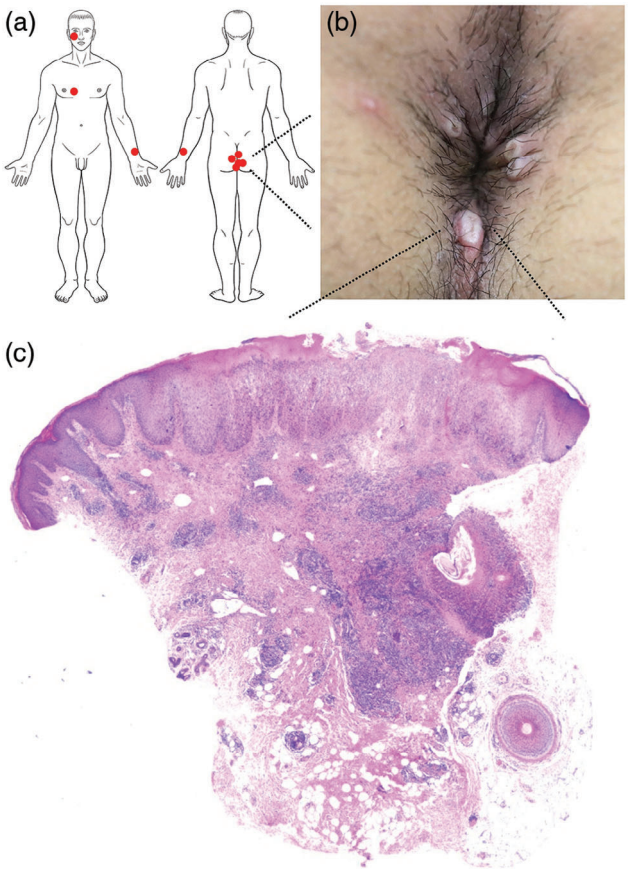

FIGURE 10 Distribution of mpox lesions, clinical picture, and histopathology findings. (a) Distribution of skin eruptions, focused on the anal region. (b) Clinical picture of deep-seated umbilicated perianal papules and pustule. (c) Hematoxylin and eosin stain (original magnification x 40).

Cowpox/catpox

"A disease discovered in some of the western counties of England, particularly Gloucestershire, and known by the name of THE COW POX", was a seminal 18th century publication by Edward Jenner, calling attention to cowpox as a human infectious disease similar to notorious smallpox.[144]

Cowpox is caused by CPXV of the genus *Orthopoxvirus*, which is endemic to Eurasia. Rodents are the natural reservoir, but CPXV can also infect other mammals, including cats, cows, dogs, elephants, or monkeys.[145–148] Zoonotic spillover to humans occurs sporadically. Cats are among the most frequent source of CPXV infection, so cowpox is also referred to as catpox.[149] Incidence rates usually peak during the late summer and early autumn.[145] Human-to-human transmission of CPXV has not been reported.

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Clinical presentation

Human cowpox occur as isolated cases or small outbreaks,[150] typically involving veterinarians or animal breeders and handlers.[150,151] The incubation period is considered 7–12 days. One or few skin eruptions usually occur at but not limited to the inoculation site, progressing from an initial macule to (sero-)papule and oftentimes ulcerative plaques or nodes with a necrotic center measuring up to > 2 cm (Figure 11). Disseminated eruptions may develop, e.g. in patients with atopic dermatitis.[152]

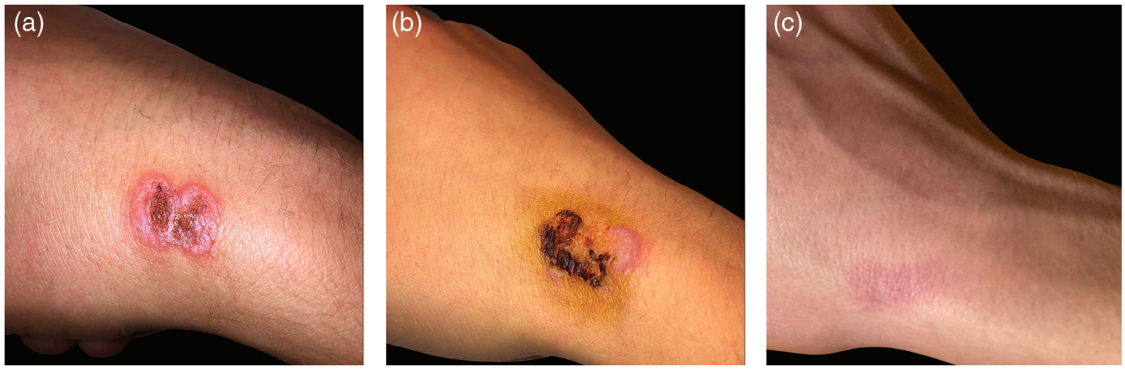

FIGURE 11 Cowpox after a farm stay. (a) two neighboring initially slightly painful, centrally ulcerative nodes with elevated margins, each approximately 2 cm in diameter followed by (b) scabbing after 1 week (brownish discoloration due to iodine), and (c) scarless healing after 4 weeks on the patient's extensor wrist (used by courtesy of J. Offermann, MD).

Disseminated eruptions may develop, e.g. in patients with atopic dermatitis.

Malaise, fever, flu-like symptoms, and/or lymphadenopathy are common accompanying symptoms. Cowpox is largely self-limiting within approximately 3 weeks. Scarring of skin eruptions may occur. Usually, no specific therapy is needed.[150,151]

Complications include colliquative and/or necrotizing lymphadenitis,[153,154] ocular cowpox,[32,38] or tonsillitis.[33] In immunocompromised individuals, case fatalities may occur[33,155] and an association between acute CPXV infection and fetal death has been reported.[156] For complicated disease, antiviral therapy can be useful. In January 2022, tecovirimat was authorized to treat cowpox under exceptional circumstances upon written request to health authorities in the EU.[134,157] Cidofovir and brincidofovir are also considered effective against CPXV infection but have not been licensed nor authorized.[158] Bacterial superinfection may require antibiotic treatment.

Disease manifestation, severity, and response to antiviral treatment depend on multiple factors, including host immunity (acquired/congenital immunosuppression and/or prior smallpox/mpox vaccination) and specific CPXV strains. Phylogenetic studies showed a large molecular virological diversity with CPXV splitting into distinct clades and lineages, similar to VACV and MPXV. As of 2023, five clades have been identified, namely clades CPXV-like 1, 2 and 3, VARV-like and VACV-like.[159,160] Distinct clades might show specific geographic distributions and virulence.[159]

Diagnosis

PCR testing allows for reliable diagnosis of CPXV infection. However, the emergence of new strains can implicate primer mismatch and false-negative results.[161] Agnostic viral metagenomics may help to overcome the hurdles of conventional sequence-dependent testing[162] in a particularly diverse species of viruses. Electron microscopy can help to detect poxvirus infection, but discrimination on the species level is challenging and availability is restricted to specialized laboratories.[5] Viral cultures, e.g. on human embryonic lung (HEL) fibroblasts[158] may serve for research purposes.

Histopathological examination of cowpox is instrumental due to CPXV-specific basophilic perinuclear proteinaceous A-type inclusion bodies, besides B-type inclusion bodies. Giemsa and/or hematoxylin-eosin staining allow for proper visualization.[12,70]

Prevention

To prevent infection, contact with infected animals should be avoided. This is particularly important for exotic (zoo) animals or new pets, which should at best be quarantined for a few days and closely observed before close contact. Primary preventive vaccination against smallpox/mpox (Table 4) is likely to prevent clinical manifestation or a severe course of cowpox due to intra-genus antigenic cross-protection. Seroprevalence studies have shown that vaccination against smallpox before eradication may no longer provide protection.[163]

Camelpox

Camelpox is a neglected zoonosis caused by camelpox virus (CMLV) of the genus *Orthopoxvirus*. The natural reservoir are Old World camelids living in semi-/arid regions of the African and Asian continent. Camelpox is among the most frequent viral infectious disease of camels[164] and was considered genus-specific for *Camelus* (*C. dromedarius* and *C. bactrianus*) until 2009, when the first cases of human camelpox were detected in India.[165,166] Zoonotic spillover usually affects camel rearers and breeders and may be due to contact to skin eruptions, but also saliva, milk, ocular, or nasal secretions of infected camels.[167] Transmission by

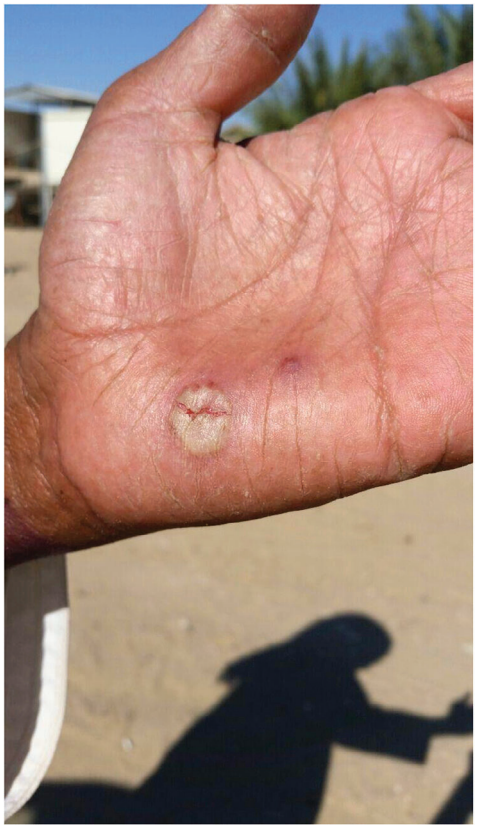

FIGURE 12 Human case of camelpox from the United Arab Emirates (UAE), used by courtesy of A. I. Khalafalla, MVSc, PhD.

camel ticks (*Hyalomma dromedarii*) has been suspected.[168] The clinical presentation of human camelpox includes the classical sequence of slightly itchy macules turning into papules, vesicles, pustules, and scabs over the course of two months.[169] Lesions usually heal without specific treatment, leaving a scar. Predilection sites are the hands and extremities (Figure 12), but mucous membranes may be involved, too.[165,167] Systemic symptoms include fever and malaise.[169]

Camelpox is a neglected zoonosis caused by camelpox virus (CMLV) of the genus *Orthopoxvirus*.

Zoonotic spillover usually affects camel rearers and breeders and may be due to contact to skin eruptions, but also saliva, milk, ocular, or nasal secretions of infected camels.

Diagnosis

If there is reasonable suspicion, the same commercially available or in-house RT-PCR test assays as used in veterinary medicine can confirm the clinical diagnosis in humans.[169] Alternatively, electron microscopy, histopathology, and/or immunohistochemistry may aid in the diagnosis but they may only be available in specialized laboratories.

Of note, another poxviral infection of camels, viz. camel contagious ecthyma (also called Auzdik disease or orf in camels), caused by an unapproved member of the genus *Parapoxvirus*, may rarely cause skin eruptions resembling camelpox in humans.[170] PCR assays targeting CMLV will usually test negative in camel contagious ecthyma patients, thus requiring specific PCR primers or electron microscopy for differentiation.[171]

Prevention

The most effective preventive measure is to avoid contact with infected animals. Vaccines for camelids are under investigation.[172]

Vaccinia and buffalopox

Vaccinia and buffalopox are caused by two closely related members of the genus *Orthopoxvirus*: VACV and buffalopox virus (BPXV), respectively.

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Vaccinia as an Adverse Event Following Immunization (AEFI)

Wild-type and laboratory-modified VACV was or has been used for vaccination against smallpox (Table 4).[173] With early-generation vaccines, the expected local reaction in immunonaive, primary vaccinees or those who have not received a smallpox vaccination for many years followed a typical course at the vaccination site: from papule on about the fifth day to vesicle formation, ulcero-necrosis with crusting and scarring (take).[174,175] Beyond that, exposure to VACV has also been associated with particular AEFI, including eczema vaccinatum, generalized vaccinia, or progressive vaccinia (formerly known as vaccinia necrosum or gangrenosum) (Figure 13).[176]

Beyond that, exposure to VACV has also been associated with particular AEFI, including eczema vaccinatum, generalized vaccinia, or progressive vaccinia (formerly known as vaccinia necrosum or gangrenosum).

Eczema vaccinatum may occur in individuals with a damaged skin barrier, e.g. in atopic dermatitis or Darier disease patients, presenting with localized or generalized papular, vesicular, pustular, or erosive rash usually within a maximum of 3 weeks following vaccination or direct/indirect exposure to a vaccinee's skin eruption(s).[177] Eczema vaccinatum can lead to critical illness, requiring intensive care and treatment such as VIG.[178] Accordingly, the indication for vaccination of individuals with damaged skin barrier,

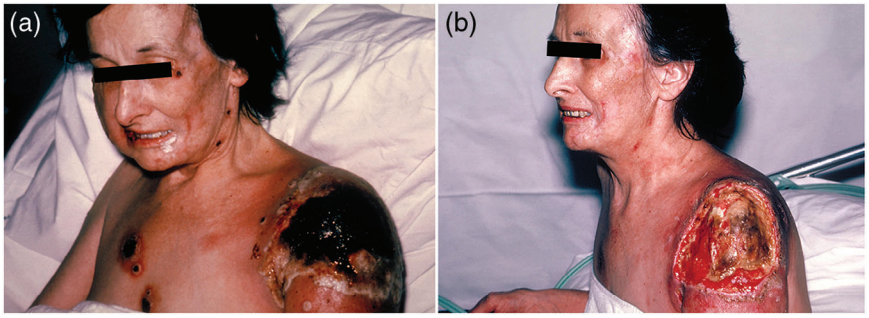

FIGURE 13 Progressive vaccinia, formerly termed vaccinia necrosum. Historical photographs showing a 62-year-old patient with chronic lymphocytic leukemia who had received the smallpox vaccine, showing (a) multilocular necrotic damage including at the vaccination site and (b) after deep wound debridement (used by courtesy of the US Centers for Disease Control and Prevention, California Department of Health Services, images deposited at the Public Health Image Library).

including major wounds, should be strictly in accordance with marketing authorization restrictions.

Generalized vaccinia is a transient disseminated vesiculo-papulo-pustular rash sometimes involving systemic symptoms such as fever, typically occurring between 4–19 days following exposure. Usually, generalized vaccinia is self-limiting, requiring no specific treatment but particular attention in immunocompromised individuals.

Progressive vaccinia (Figure 13) mainly occurs in individuals with impaired cell-mediated immune response, allowing for uncontrolled viremia and sometimes fatal outcome due to secondary complication such as sepsis.[177,179]

Table 5 provides published consensus case criteria for eczema vaccinatum, generalized, and progressive vaccinia as AEFI.[177]

Incidence rates of eczema vaccinatum, generalized vaccinia, and progressive vaccinia in the general population date back from the pre-eradication era and must be interpreted with caveats. Historical incidence rates for eczema vaccinatum ranged from 10–38.5/1 million primary vaccinees[178,180,181], for generalized vaccinia from 23.4–241.5/1 million primary vaccinees[180,181], and for progressive vaccinia approximately 1/1 million vaccinees.[179] Incidence rates are considered lower in re-vaccination candidates.[180,181]

Measures prior to vaccination using a replication-competent vaccine derived from vaccinia virus (VACV)

Vaccinia can be transmitted from a vaccinee who received a replication-competent VACV-derived vaccine to vulnerable individuals. Therefore, assessing and informing candidates for vaccination should include:

- Members of the household with damaged skin barrier/chronic skin disease are susceptible to infection.
- Covering of the inoculation site until resolution of the skin eruption is recommended.
- Strict hygiene measures, such as hand washing with soap and/or use of disinfectant and separate waste disposal of potentially infectious items can help to prevent transmission.

Depending on regional laws, reporting of an adverse event following immunization (AEFI) in the context of vaccinovigilance may be mandatory.

Vaccinia following natural infection

Historically, natural VACV infection was a veterinary infectious disease affecting cattle but with limited significance in humans.[182,183] In the 1990s however, natural VACV infection leading to vaccinia in dairy workers emerged in Brazil, mainly in the Atlantic Forest region where extensive farming is practiced.[183] In spatio-temporal relation to bovine outbreaks, vaccinia affects farmers presenting with a typical sequence of multiple itchy or painful skin eruptions starting as a macule, then progressing from papule over vesicle to (umbilicated) pustule, ulcer, and scab. Eruptions are usually located on hands, arms, legs, and less frequently the face. Concomitant or prodromal symptoms include fever, malaise, myalgia, and/or localized lymphadenopathy. The most common complication may be bacterial superinfection, leading to sick leave and economic loss.[182–186] VACV infection may be asymptomatic in a relatively large proportion of cases.[186] Diagnosis is usually based on the patient's history, which suggests direct contact with infected cattle. PCR, histopathology, and electron microscopy (available in specialized laboratories) can support the diagnosis. Of note, dual infection with VACV and PCPV has been reported in a dairy worker with severe disease, but the clinical relevance of such multiple infections needs to be investigated.[187]

Historically, natural VACV infection was a veterinary infectious disease affecting cattle but with limited significance in humans.

In the 1990s however, natural VACV infection leading to vaccinia in dairy workers emerged in Brazil, mainly in the Atlantic Forest region where extensive farming is practiced.

Usually, supportive and topical treatment can sufficiently relieve discomfort until healing within approximately 3 weeks.

The vaccinia virus undergoes relatively fast evolutionary changes[188] leading to diversification and subsequently, classification of different VACV strains, such as Cantagalo[184],

TABLE 5 Case criteria for eczema vaccinatum, generalized, and progressive vaccinia as AEFI, adapted from.[177].

	Probable case	Confirmed case
	An individual who has received a VACV-derived vaccine within the last < 21 days or a known close contact of a recent vaccinee with:	
Eczema vaccinatum	Past or current exfoliative skin condition, e.g. atopic dermatitis AND Multiple skin lesions, which are distant from the vaccination/exposure site AND Are or become vesicular/ pustular/ erosive/ ulcerative AND Other etiologies have been excluded	Criteria consistent with 'probable case' AND Laboratory evidence of concurrent VACV infection distant from vaccination/exposure site by culture OR PCR/ NGS detection OR Antigen detection OR Histopathological examination AND Electron microscopy (ideally to be confirmed by subsequent culture)
Generalized vaccinia	Vesicular or pustular eruption at ≥ 1 body area distant from the vaccination/exposure site AND Lesions follow approximately the typical progression from papule to vesicle, pustule, scab, and scar AND Autoinoculation does not account for skin eruption AND Other etiologies have been excluded	Criteria consistent with 'probable case' AND Laboratory evidence of concurrent VACV infection distant from vaccination/exposure site by culture OR Histopathological examination AND PCR/NGS detection OR Antigen detection OR Electron microscopy (ideally to be confirmed by subsequent viral culture)
Progressive vaccinia	Known or suspected depressed or defective immune system AND A vaccination/exposure site lesion with No or minimal surrounding inflammation associated with non-healing or enlarging lesion OR Progressive expansion ≥ 21 days after vaccination/exposure OR Failure to heal or to regress ≥ 21 days after vaccination/exposure AND Other etiologies have been excluded	Known or suspected depressed or defective immune system AND A vaccination/exposure site lesion with No or minimal surrounding inflammation associated with non-healing or enlarging lesion OR Progressive expansion ≥ 15 days after vaccination/exposure OR Failure to heal or to regress ≥ 15 days after vaccination/exposure AND Other etiologies have been excluded AND Laboratory evidence of concurrent VACV infection by culture OR Histopathological examination AND PCR/NGS detection OR Antigen detection OR Electron microscopy (ideally to be confirmed by subsequent viral culture)

Abbr.: AEFI, adverse event following immunization; NGS, next-generation sequencing; VACV, vaccinia virus

Araçatuba,[182] or Passatempo virus.[189] Different strains show distinct virulence and potentially varying susceptibility to antiviral treatment.[190]

To date, it remains unclear whether those strains are vaccine-escape strains resulting from the smallpox vaccination program by the Pan American Health Organization (PAHO) and WHO or whether they have naturally evolved ever since the introduction of poxviruses to the New World in the 16th century.[183]

Buffalopox

Buffalopox is caused by BPXV, a VACV-like strain endemic to India. Zoonotic spillover infection from buffalos usually affects dairy workers but has also been implicated in nosocomial outbreaks on burn units in India.[191] Symptoms resemble those of Brazilian vaccinia.[34,191–194] Among the presumed characteristic features are relatively large skin eruptions (> 1 cm)[191] and enoral manifestation.[193]

Buffalopox is caused by BPXV, a VACV-like strain endemic to India.

Zoonotic spillover infection from buffalos usually affects dairy workers but has also been implicated in nosocomial outbreaks on burn units in India.

Prevention

Avoiding risk contacts with infected animals represents the safest prevention strategy. VACV, BPXV, and other VACV-like strains all belong to the genus *Orthopoxvirus*, so currently approved smallpox/mpox vaccines should prevent severe disease. However, individuals who were vaccinated before the cessation of the smallpox vaccination program in 1980 may no longer be protected.[186] Vaccination of cattle is currently under investigation. Caution should be exercised when handling or consuming raw milk cheese or dairy products and animal fats, such as ghee, which may result in transmission of VACV/VACV-like strains and cause symptomatic disease.[191,195]

MOLLUSCIPOXVIRUS INFECTION

The genus *Molluscipoxvirus* comprises one single species: MOCV, causing molluscum contagiosum (water warts). The pathogen is host-specific and occurs primarily in humans (anthroponosis). Four MOCV genotypes associated with clinically indistinguishable presentation have been identified. The most common subtype is MOCV-1, followed by MOCV-2.[196,197] MOCV-2 appears to be more frequently detectable in genital infections.[198]

The viral infection remains confined to keratinocytes of the epidermal *stratum spinosum*. MOCV occurs worldwide with an estimated incidence of 5%–18% and a higher prevalence suspected in the tropics and subtropics.[199] The majority of those infected are children of pre-school and primary school age. MOCV infections can be observed in small epidemics in community settings. The infection is transmitted directly through close physical contact, including sexual contact, autoinoculation, or indirectly through fomites.[200]

The infection is transmitted directly through close physical contact, including sexual contact, autoinoculation, or indirectly through fomites.

Clinical presentation

MOCV infection leads to formation of a skin-colored or reddish dome-shaped papule with a central umbilication (Figure 14).

MOCV infection leads to formation of a skin-colored or reddish dome-shaped papule with a central umbilication.

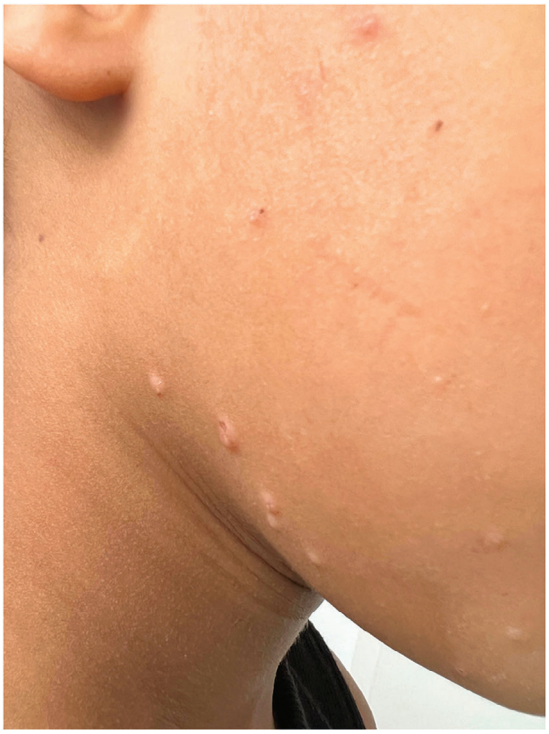

FIGURE 14 Molluscum contagiosum. Multiple umbilicated skin-colored papules on the face of a patient with Fitzpatrick skin type IV (used by courtesy of M. Alex, MD).

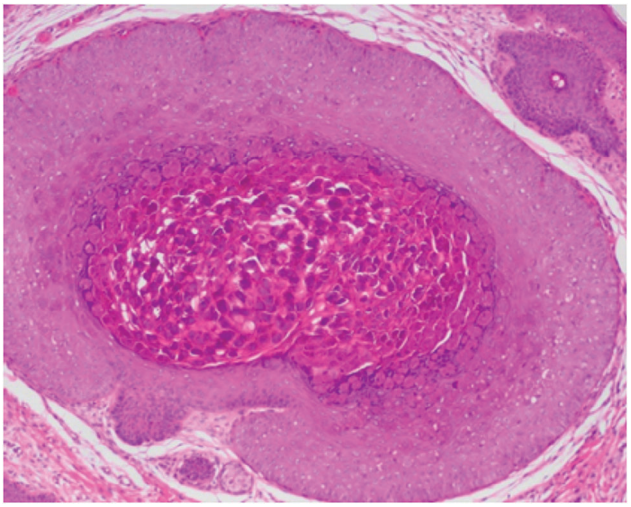

FIGURE 15 Histology of molluscum contagiosum (hematoxylin and eosin stain). Inverted epithelium with large molluscum bodies (original magnification x 40).

When pressure is applied to a lesion, whitish, granular material is discharged, containing highly infectious MOCV corpuscles. These can also be visualized histologically (Figure 15). Single or grouped 0.2–0.6 cm papules develop, often with scattered seeding over the entire integument with emphasis on neck, upper body, upper arm and axillary fold, also on the face, anogenital area, and hands. In severe

cases, there is eruptive generalized occurrence of lesions (eczema molluscatum). Mollusca contagiosa are observed particularly frequently in younger children, especially in children with xerosis cutis in atopic diathesis. Pre-treated lesions or lesions that are already in regression are often surrounded by local dermatitis and eczematization. Hypersensitivity reactions with a papular acrodermatitis called Gianotti-Crosti syndrome-like reaction (GCLR) have been reported in a subgroup of younger, mostly male children and adolescents.[201,202]

In adults, single but significantly larger (5–10 mm) mollusca occur, often in the anogenital and pubic region.[203] Rarer sites of infection are perioral and oral mucous membranes and cervix. Sometimes, giant mollusca are found, especially in immunocompromised patients. Other clinical presentations may resemble cystic, ulcerated, or pseudolymphomatous lesions. Disseminated findings without a significant tendency to regression occur primarily in the case of local (atopic diathesis) or systemic immunodeficiency (e.g., tumor disease, iatrogenic or hereditary immunosuppression, HIV infection). Severe MOCV infections with ocular involvement (keratitis) and skin necrosis may manifest in the context of immunodeficiency, especially in the late stages of untreated HIV infection and in the context of immune reconstitution syndrome (IRIS).[204–206]

Severe MOCV infections with ocular involvement (keratitis) and skin necrosis may manifest in the context of immunodeficiency, especially in the late stages of untreated HIV infection and in the context of immune reconstitution syndrome.

Diagnosis

Due to the characteristic clinical picture, a visual diagnosis is often possible. Dermatoscopy or in vivo confocal microscopy may be helpful. Histological confirmation can be performed. The characteristic picture shows inverted lobules of squamous epithelium with mollusca bodies maturing towards the surface. The lobules may be separated by fine septa (Figure 15). PCR testing and electron microscopy are available for detection, but are not routinely used in clinical practice.

Prevention and therapy

The disease is often self-limiting after 6–60 months due to the development of specific immunity and treatment is not always required. Avoidance of microtrauma and smear infections are preventive measures. Patients or parents/caregivers must be informed about risks of autoinoculation and advised against excoriation and squeezing papules to prevent further spread of lesions.[207,208] Towels, bed-linen, or clothes should not be shared. Basic moisturizing therapy, especially for atopic skin, is essential for the prevention of MOCV infection. In case of eczematization, e.g. with underlying skin barrier dysfunction (atopic dermatitis, etc.) or secondary eczematization around the mollusca, class I–II or higher topical corticosteroids may be used.[209] Likewise, parainfectious GCLR can be successfully treated with topical corticosteroids or short-term systemic corticosteroids.[201,202] The use of corticosteroids in viral diseases such as molluscum contagiosum is controversial because of their immunosuppressive effects.[210,211] However, careful topical application to restore the skin's protective barrier, relieve itching and prevent autoinoculation around molluscs is guideline-based practice.[208]

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In patients with anogenital involvement, mechanical hair removal (e.g. shaving, sugaring, waxing, threading) in the respective area should be avoided.[212–214] If sexual transmission is suspected, other STIs should be excluded.[208] Therapeutic options include ablative measures such as curettage, laser, or cryotherapy. Local treatments may include potassium hydroxide solution, vitamin A acid, lactic acid, salicylic acid preparations as creams, benzoyl peroxide, tea tree oil, and podophyllotoxin 0.5%, often associated with irritation of the surrounding skin. The administration of imiquimod 5% is controversial and often leads to severe local irritation. Ingenol mebutate gel, originally intended for the treatment of actinic keratoses, is or has been used off-label in several countries for the treatment of mollusca contagiosa. However, its marketing authorization in the EU has been suspended since 2020 due to potential carcinogenic effects. Therefore, its use for mollusca contagiosa must also be considered obsolete, at least in the EU.[215] Especially in immunocompromised patients, cidofovir gel is used, sometimes leading to cure with the development of severe irritation.[208,216,217]

PARAPOXVIRUS INFECTION

Parapoxvirus infection, also known as farmyard pox, includes orf, milker's nodule, and bovine papular stomatitis virus (BPSV) infection, which may be clinically indistinguishable.[218]

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Orf (ecthyma contagiosum, contagious pustular dermatitis)

Orf is caused by ORFV, which infects sheep and goats as natural reservoir.[219,220] Phylogenetic analyses have shown that ORFV sequences predominantly cluster into two clades:

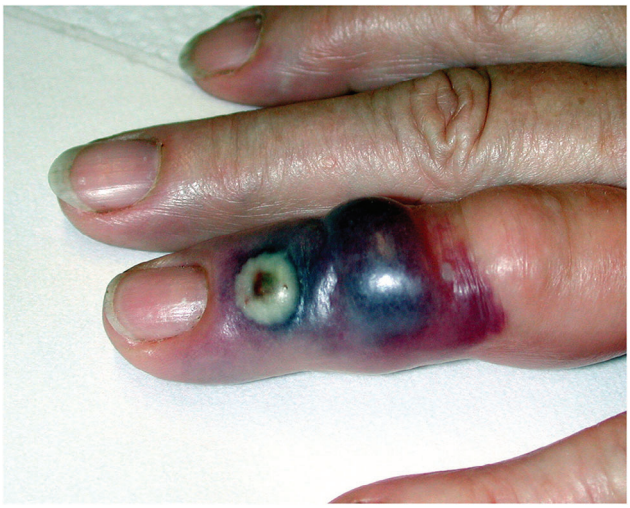

FIGURE 16 Orf on the forefinger of a farmwoman from a German rural county. Pustule with necrotic center on dark livid hemorrhagic ground, adjacent to a hemorrhagic node with incipient central umbilication, edema of the forefinger (used by courtesy of A. Stich, MD, MSc, DTMH).

type S (for sheep) and type G (for goat), consistent with the reservoir of isolates. Human orf is predominantly caused by type S; therefore, sheep are considered to be the major source of human orf.[221] One of the first descriptions of occasional human orf dates from 1934.[222] Nowadays, zoonotic spillover causing human disease due to contact with infected animals is reported frequently and worldwide. Orf usually affects farmers, butchers, but also people attending mass gatherings with close animal contact, e.g. during the Muslim holiday Eid al-Adha ("Feast of the Sacrifice").[219,220,223–225] Accordingly, an incidence peak can be observed in summer.[219] Human-to-human transmission has been reported.[226]

Orf is caused by ORFV, which infects sheep and goats as natural reservoir.

Clinical picture

After an incubation period of 3–7 days,[227] ORFV infection leads to one or few initially reddish or violaceous macules which then progress to sometimes painful, targetoid plaques or dome-shaped nodes with central necrosis on edematous ground, usually localized on the hands. Exophytic tumors can be highly vascularized. The accompanying inflammatory reaction can be movement-restricting when near a joint (Figure 16). Orf is largely benign and self-limiting. Skin eruptions develop a dry scab which falls off within 3–6 weeks. Systemic symptoms such as fever or lymphadenopathy occur infrequently. Locoregional supportive therapy is often sufficient.[219,220,223,228]

After an incubation period of 3–7 days, ORFV infection leads to one or few initially reddish or violaceous macules which then progress to sometimes painful, targetoid plaques or dome-shaped nodes with central necrosis on edematous ground, usually localized on the hands.

Atypical presentations and complications include ocular[35] or giant orf.[229] Giant orf mainly occurs in immunocompromised individuals, where exophytic, raspberry-like tumors reach a diameter of > 5–6 cm.[229–232] As of 2023, there is no licensed or authorized antiviral treatment for orf. Anecdotal reports of treatment for complicated orf include cidofovir or imiquimod cream,[233,234] cryotherapy,[235] and surgical excision.[230] Successful treatment of ocular orf was reported with 0.5% idoxuridine ointment.[35]

Parainfectious reactions

ORFV infection is known for parainfectious, immune-mediated phenomena such as vesiculobullous efflorescences, type IV hypersensitivity reactions, and photoaggravated eruptions.[228,236,237] The observed vesiculobullous reaction pattern includes orf-induced immunobullous disease,[238] epidermolysis bullosa acquisita,[239] erythema exsudativum multiforme,[240] and bullous pemphigoid, including mucous membrane pemphigoid.[241,242] Parapoxvirus-specific viromimetic proteins (see chapter "Poxvirus interactions with the host"), such as viral vascular endothelial growth factor (VEGF), probably play a critical role in the development of an antibody-mediated (including IgA, C3, IgG, especially anti-laminin-332[243]) and/or cytotoxic T-cell-mediated immune response. In a 2023 review, the majority of parainfectious orf-associated reactions occurred 3 weeks after orf onset.[228] Treatment modalities include topical and systemic glucocorticoids (0.5–1 mg/kg body weight prednisolone equivalent) and antihistamines for pruritus. These immune-mediated phenomena usually resolve within about 2 weeks without complications.[228,236,237]

ORFV infection is known for parainfectious, immune-mediated phenomena such as vesiculobullous efflorescences, type IV hypersensitivity reactions, and photo-aggravated eruptions.

Milker's nodule (paravaccinia)

Milker's nodule, also known as paravaccinia, is caused by pseudocowpox virus (PCPV), which primarily infects cattle worldwide but can spill over to humans, mainly via direct contact.[244] The incubation period of milker's nodule is 5–15 days, on average. The clinical signs and symptoms resemble orf (Figure 17). Usually, milker's nodules heal within 3–6 weeks, without scarring.[245] PCPV infection can rarely lead to erythema exsudativum multiforme.[246]

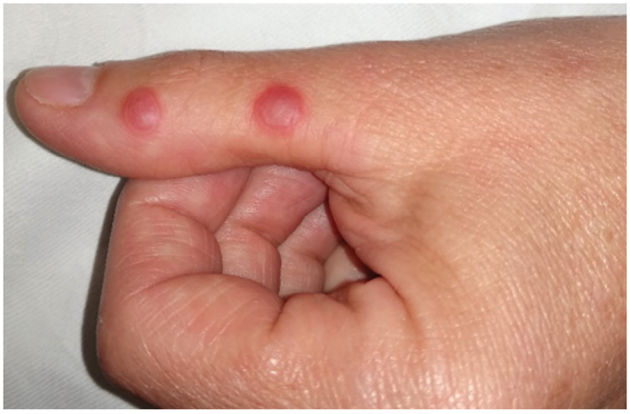

FIGURE 17 Milker's nodule. Two solitary round erythematous nodules on the dorsal thumb with minimal surrounding inflammation (used with permission of Deutscher Ärzteverlag GmbH, from Marckmann D, Frasnelli A: Milker's nodule (pseudocowpox) in a female patient following a calf bite. *Dtsch Arztebl Int*. 2020;117:870; permission conveyed through Copyright Clearance Center, Inc.)

Milker's nodule, also known as paravaccinia, is caused by pseudocowpox virus (PCPV), which primarily infects cattle worldwide but can spill over to humans, mainly via direct contact.

Bovine papular stomatitis virus (BPSV) infection

The natural reservoir of BPSV are cattle around the globe, where infection is often asymptomatic or very mild, thus leading to oftentimes unexpected spillover to humans handling infected animals.[247–249] In general, little importance is attributed to BPSV infections in humans. In the 1970s however, a survey among veterinary students indicated that BPSV infections are likely underdiagnosed in at-risk groups.[250] The incubation period may be similar to orf and milker's nodule, and the clinical presentation and course are also indistinguishable.

The natural reservoir of BPSV are cattle around the globe, where infection is often asymptomatic or very mild, thus leading to oftentimes unexpected spillover to humans handling infected animals.

Diagnosis

Orf, milker's nodule, and BPSV infection are neglected zoonoses. The first step towards the diagnosis of farmyard pox is a thorough patient assessment, including and focusing on farm animal contact and/or occupation of the patient (e.g., butchers).[224,225,245]

For laboratory confirmation, RT-PCR is the mainstay method. Viral cultures, e.g., on bovine Sertoli cells, can serve for research purposes.[251] Serology testing may not be suitable for detecting acute infection but for seroprevalence studies.[252,253] Histopathological examination will not allow to differentiate between different genera of poxviruses.[254] Electron microscopy may only be available in specialized laboratories but can be instrumental to detect parapoxvirus infection for their particular cocoon-shape and wafer-like surface as opposed to brick-shaped poxvirus particles of all other genera.[5,251]

Prevention

Primarily, avoidance of risk contacts prevents infection. Especially in case of occupational exposure risk, protective gloves should be worn, and disinfectants or soap and water be used to clean udders and teats, for example.[223,244] There is no approved vaccine against parapoxvirus for human use. Smallpox/mpox vaccination will not induce cross-protection against farmyard pox. A parapoxvirus vaccine is available for veterinary use, based on non-attenuated, live virus preparations.[255] Caution is required when handling freshly vaccinated animals to prevent spillover.[256]

YATAPOXVIRUS INFECTION

Tanapox and Yaba-like disease are rare viral zoonoses primarily endemic to Equatorial and East Africa, caused by tanapox virus (TANV) or Yaba-like disease virus (YLDV), respectively. Both belong to the genus *Yatapoxvirus*.[6,257,258]

Tanapox and Yaba-like disease are rare viral zoonoses primarily endemic to Equatorial and East Africa, caused by tanapox virus (TANV) or Yaba-like disease virus (YLDV), respectively. Both belong to the genus *Yatapoxvirus*.

The most probable natural reservoir of TANV are non-human primates. Transmission to humans may be vector-borne. The prevalence of tanapox has been correlated with activity patterns of culicine mosquitos (species: *Mansonia*) in the Tana River valley, similar to West Nile virus circulation during flood periods.[43] Climate change and other anthropogenic environmental changes may be contributing to alterations in the epidemiology of tanapox: Whereas previously tanapox was always detected in an area 10° south or north of the equator, in 2022 a probable autochthonous TANV infection was reported from South Africa's Kruger National Park, Limpopo Province (24° south of the equator).[259]

The most probable natural reservoir of TANV are non-human primates. Transmission to humans may be vector-borne.

To date, there has been no clear evidence of human-to-human transmission.

Yaba-like disease virus is closely related to TANV and is therefore referred to as TANV strain Davis.[6] The most probable natural reservoir of YLDV (TANV strain Davis) are non-human primates in African tropical rainforest regions (Yaba is a suburb of Lagos, Nigeria). Zoonotic infection has

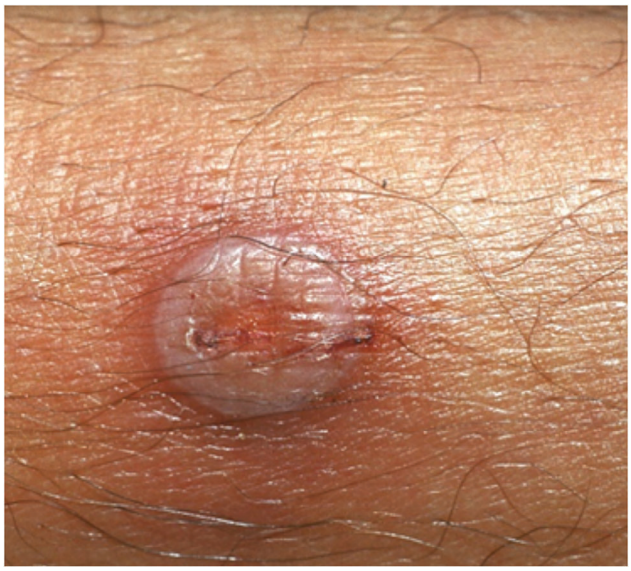

FIGURE 18 Tanapox in a traveler returning from Tanzania.[258] Solitary node measuring approximately 14 mm with central umbilication on erythematous ground on the lower leg (used by courtesy of A. Stich, MD, MSc, DTMH).

been reported in zookeepers bitten or scratched by monkeys, causing mild and self-limiting symptoms similar to tanapox.[260,261]

The most probable natural reservoir of YLDV (TANV strain Davis) are non-human primates in African tropical rainforest regions (Yaba is a suburb of Lagos, Nigeria).

Clinical presentation

Tanapox was first described in the context of an epidemic of febrile illness occurring among children in a flooded rainforest village along Kenya's largest river, the River Tana, in September 1957. All children affected developed one or two smallpox-like skin lesions and some were transferred to a hospital in Mombasa, Kenya's most important port city on the Indian Ocean. Healthcare experts recognized distinctive features of the yet unknown disease, viz. the small number of relatively large and firm papules or nodules mainly affecting the face, neck, and trunk but usually sparing extremities as well as slow progression and the absence of pustulation.[262,263] Tanapox patients may experience tenderness of skin lesions, headache, backache, fatigue, and local lymphadenopathy. Usually, tanapox lesions heal within 6-8 weeks, leaving a scar.[257,258,263,264] Figure 18 shows a solitary tanapox lesion from a 49-year old traveler returning from Tanzania in 1999.[258]

Diagnosis

Both tanapox and Yaba-like disease are neglected tropical zoonoses. When assessing medical history, the itinerary should be considered, as well as the time of travel (rainy or dry season) and possible animal contacts. Laboratory testing is required to make the diagnosis of tanapox and/or Yaba-like disease. Highly specific and sensitive RT-PCR assays are available for the detection of TANV and YDLV in designated diagnostic facilities.[265] Also, convenient multiplex PCR assays have been developed to test for a variety of ortho- and yatapoxviruses.[257] Viral cultures, e.g. on monkey kidney cells, showing cytoplasmic granulation, nuclear vacuoles, and B-type inclusions may serve for research purposes.[266]

When assessing medical history, the itinerary should be considered, as well as the time of travel (rainy or dry season) and possible animal contacts.

Prevention and therapy

For prevention, use of repellents and insect protection are key, especially during the evening and night hours when *Culex* mosquitos are most active.[267] As of 2023, there is no primary preventive vaccination against yatapoxviruses. Vaccination against orthopoxviruses is not considered to induce cross-protection. There is no licensed antiviral for yatapoxvirus infection in humans but cidofovir and brincidofovir may be among candidates for treatment.[268]

RISK FACTORS FOR POXVIRUS INFECTIONS

Systematic investigation of factors associated with an unfavorable outcome of poxvirus infection is sparse, but historical data and small case series/case reports suggest possible risk factors.

Extremes of age

Mpox attack and mortality rates were highest among children aged < 10 years.[269] During the 2022/2023 mpox outbreak however, children have rarely been affected, leaving attack and mortality rates among children unclear in this context.[270] Old age has been associated with severe outcome in smallpox.[271]

Historical evidence from previous smallpox and mpox outbreaks in endemic countries has shown that extremes of age are considered risk factors for severe outcome.

Skin barrier disruption/dysregulation

A disrupted or dysregulated skin barrier has frequently been associated with severe disease manifestation. Among dermatological patients at risk are those with atopic dermatitis[150,272] or Darier disease[273] but also burn patients.[191,274,275] Viral dissemination and/or inadvertent inoculation, e.g. eczema molluscatum or eczema vaccinatum can severely impair quality of life and lead to long-term sequelae.[272] Dermatological treatment for a disrupted/dysregulated skin barrier, such as topical corticosteroids[210,211] or calcineurin inhibitors[276] showed incongruent therapy successes, partly with deterioration of poxviral infection. The cautious use of topical corticosteroids on eczematous skin is consistent with guidelines, e.g. in molluscum contagiosum to restore the skin barrier, relieve pruritus, and prevent autoinoculation.[208] Lipid-replenishing basic therapy and certain biologics (e.g., dupilumab) may facilitate viral clearance.[208,277–279]

A disrupted or dysregulated skin barrier has frequently been associated with severe disease manifestation.

Among dermatological patients at risk are those with atopic dermatitis or Darier disease but also burn patients.

Immunosuppression

Primary immunodeficiency syndromes often manifest in childhood, e.g. indicated by a severe course of an actually benign poxvirus infection, such as molluscum contagiosum: For example, eczema molluscatum is typical of congenital dedicator of cytokinesis 8 (DOCK8) deficiency, a combined immunodeficiency syndrome.[280,281]

Pre-existing immunodeficiency is a relevant risk factor for severe disease.

Unusually severe and/or multiple concomitant viral infections and/or poor response to (antiviral) therapy should raise suspicion of immunodeficiency.

Unusually severe and/or multiple concomitant viral infections and/or poor response to (antiviral) therapy should raise suspicion of immunodeficiency.[282] Relevant secondary immunodeficiency includes HIV infection. Based on lessons learnt from the 2022/2023 mpox outbreak, HIV-positive individuals, particularly those who are inadequately treated with antiretroviral therapy, may be at risk of severe and fatal disease.[283] Similar observations were made for cowpox[284,285] and molluscum contagiosum.[286]

Patients with hematological malignancy and/or transplant patients are also at increased risk, requiring careful monitoring and timely consideration of antiviral therapy or primary preventive vaccination in accordance with regulatory approvals and depending on contraindications (Table 4).[231,287–289]

Certain autoimmune diseases associated with dysfunctional humoral and cellular immune response, e.g. systemic lupus erythematosus or sarcoidosis, are highly associated with viral infections[290] and may also be associated with complicated poxvirus infection, as has been reported for molluscum contagiosum.[291,292]

Within the dermatological patient population, those who receive iatrogenic immunosuppressive therapy including biologic therapy, e.g., due to psoriasis, bullous dermatoses, or lymphoma, should be emphasized. Complicated poxvirus infections were described for the use of oral tacrolimus, mycophenolate mofetil, prednisone,[289] methotrexate,[293] and anti-TNF-α therapy.[230,294]

Within the dermatological patient population, those who receive iatrogenic immunosuppressive therapy including biologic therapy, e.g., due to psoriasis, bullous dermatoses, or lymphoma, should be emphasized.

Pregnancy

Pregnant women, especially during the first two trimesters, are at risk for fetal death or congenital defects of the baby as has been shown for mpox, cowpox, vaccinia, and smallpox.[102,156,295–297] Of note, highly prevalent MOCV infection has never been reported to be associated with fetal death or congenital defects.

Pregnant women, especially during the first two trimesters, are at risk for fetal death or congenital defects of the baby as has been shown for mpox, cowpox, vaccinia, and smallpox.

FUTURE PERSPECTIVES AND A VIEW BEYOND DERMATOLOGY

Poxvirus infections are more than a marginal note in the history book, but a notable PHEIC, neglected tropical dermatosis, STI or childhood disease, or a souvenir from the last farm visit or vacation trip.

The clinical spectrum of poxvirus infections is continuously evolving, with new viruses emerging, e.g. infection with yet unassigned Alaskapox virus in an Alaskan patient,[298] Akhmeta virus in Georgian milkers,[299,300] or sealpox in a marine mammal technician.[301]

Considering the origins of zoonotic poxvirus infections, the implications go beyond human dermatology: On camel farms in the arid regions of the Old World, on Brazilian farmlands, or on Indian buffalo ranches, poxvirus infections lead to considerable economic setbacks, e.g. due to reduced milk yields and/or animal mortality.[167,186] Another example is crocodile farms where the leather affected by crocodilepox (Figure 19), a poxvirus species closely related to mollusci- and parapoxviruses (Figure 1), brings losses.[302]

A first step has been made with the first-in-class antiviral tecovirimat, but there are concerns about the rapid development of resistance mutations. New or repurposed

TABLE 6 Overview of infectious differential diagnoses of poxvirus infections of the human skin.

Disease	Pathogen	Hotspots	Incubation	Clinical picture	Diagnostics*	Complications	Treatment**
Cutaneous Anthrax	*Bacillus anthracis*	Central and South America, Sub-Saharan Africa, Central and Southwestern Asia, Southern and Eastern Europe	1–7 days	Vesicle(s), papule(s), pustule(s) ("malignant pustule") at inoculation site (usually a wound), itch, swelling, development of painless ulcer(s) with necrotic eschar, lymphadenitis	Microscopy, bacterial culture, PCR, NGS, serology, histopathology	Scarring, disseminated infection, fever, malaise, delirium, death	Usually self-limiting, antibiotics (e.g., penicillin, doxycycline)
Buffalopox	BPXV	India	3–19 days	Fever for 2–3 days, followed by umbilicated papule(s) and/or nodule(s), sometimes containing pustular material, size may be up to 1 cm in diameter	PCR, NGS, electron microscopy, histopathology	Scarring, bacterial superinfection, conjunctivitis	Usually self-limiting within 3 weeks
Camelpox	CMLV	North Africa, Arabian Peninsula, South Asia, including India	3–19 days	Fever for 2–3 days, followed by umbilicated papule(s) and/or nodule(s), sometimes containing pustular material, size may be up to 1 cm in diameter	PCR, NGS, electron microscopy, histopathology	Scarring, bacterial superinfection	Usually self-limiting within 3–8 weeks
Chickenpox	HHV-3 (VZV)	Worldwide	14–16 days	Fever, flu-like symptoms, malaise → widespread itchy vesicular rash ("dewdrop on a rose petal") with pink/reddish papules, and scabs on erythematous ground, often starting on trunk/ face	Clinical diagnosis, PCR, NGS, serology, microscopy/ Tzanck smear	Scarring, bacterial superinfection, pneumonia, encephalitis, Ramsay Hunt syndrome, ocular complication (e.g., keratitis, uveitis)	Usually self-limiting within 3 weeks, antiviral treatment (e.g., acyclovir)
Cowpox	CPXV	North Asia, Northern Europe	7–12 days	Usually, one large painful macula → papule → vesicle → pustule with hard necrotic eschar, surrounding edema and erythema, fever and lymphadenopathy may be present	PCR, NGS, electron microscopy, histopathology (A-type inclusion bodies)	Scarring, disseminated infection, ocular lesions, bacterial superinfection	Usually self-limiting within 3 weeks, antiviral treatment (e.g., tecovirimat, cidofovir, brincidofovir)

(Continues)

TABLE 6 (Continued)

Disease	Pathogen	Hotspots	Incubation	Clinical picture	Diagnostics*	Complications	Treatment**
Farmyard pox (orf, milker's nodule, bovine papular stomatitis)	ORFV, PCPV, BPSV	Worldwide	2–7 days (milker's nodule up to 15 days)	Usually, < 5 papules on the hands, sometimes maculopapular rashes, target lesions, fever, lymphadenopathy	PCR, NGS, electron microscopy, Tzanck smear (B type inclusion bodies), histopathology	Scarring, very large lesions (e.g., Giant Orf) disseminated infection, ocular lesions, erythema exsudativum multiforme, bullous pemphigoid, Stevens-Johnson syndrome, bacterial superinfection	Usually self-limiting within 4–8 weeks
Hand, foot, and mouth disease	EV-A	Worldwide	3–6 days	Fever, flu-like symptoms, diarrhea, mouth sores, and skin rash with painful flat, angular papules → polygonal vesicles with a reddened halo → pustules, especially on palms and soles, sometimes lymphadenopathy	PCR (stool!), NGS, electron microscopy, Tzanck smear, histopathology	Onychomadesis, high fever	Usually self-limiting within 1–2 weeks
Herpes simplex	HHV-1/-2 (HSV-1/-2)	Worldwide	3–7 days	Painful and/or itchy vesicles and/or ulcers on erythematous ground, fever, body aches and lymphadenopathy may be present	Clinical diagnosis, PCR, NGS, serology, Tzanck smear	Herpetic gingivostomatitis or pharyngotonsillitis of primary infection, recurrent or disseminated infection, meningoencephalitis, ocular manifestation, bacterial superinfection	Usually self-limiting within 1–2 weeks, antiviral medication (e.g., acyclovir, famciclovir, valacyclovir)
Cutaneous Leishmaniasis	Leishmania (Viannia)	Old World (Asia, Middle East, North Africa, Southern Europe), New World (Mexico, Central/South America)	1 week to several months or years	Papule → indolent ulcerated nodule or plaque → → depressed scar	Clinical diagnosis, PCR, NGS, histology, Tzanck smear (Leishman-Donovan bodies)	Scarring, spread to mucous membranes (mucocutaneous Leishmaniasis), ocular complications, bacterial superinfection	Usually self-limiting within months or years, treatment modalities are discussed controversially but may include thermotherapy, pentavalent antimonials, azoles, and miltefosine

(Continues)

TABLE 6 (Continued)

Disease	Pathogen	Hotspots	Incubation	Clinical picture	Diagnostics*	Complications	Treatment**
Lymphogranuloma venereum (LGV)	*Chlamydia trachomatis* serovars L1-L3	Worldwide	1–6 weeks	Stage I: anogenital primary lesion (papule, vesicles, ulceration), often proctitis and proctocolitis Stage II: inflammatory lymph node complex, abscesses and fistulas, general symptoms (fever, malaise) Stage III: anorectal symptom complex with fistula formation, strictures and scarring	NAAT (PCR) and genotyping for L-serovars, serology (only if NAAT is not available)	Hemorrhagic proctocolitis, irreversible fistula formation, strictures and scarring, lymphoedema	Doxycycline 100 mg BID p.o. $\geq$ 21 days
Measles	MeV	Worldwide	10–12 days	Fever and flu-like symptoms, Koplik spots, conjunctivitis → maculopapular rash starting in the face, then spreading all over the body, including palms/soles	PCR, NGS, serology, histology	Pneumonia, meningitis/encephalitis (including SSPE/ Dawson disease), blindness, hemorrhage, miscarriage	Usually self-limiting
Molluscum contagiosum	MOCV	Worldwide	2–8 weeks	Small white, pink, or flesh-colored papule(s) with central umbilication, rarely located on palms/soles; genitoanal involvement in adults (STI)	Tzanck smear (Henderson-Patterson bodies)	Scarring, bacterial superinfection, Gianotti-Crosti syndrome-like reaction	Usually self-limiting within months to years
Mpox	MPXV	Worldwide	5–21 days	Malaise, flu-like symptoms, lymphadenopathy, sometimes fever, followed by either a sequence of usually multiple painful and/or itchy → macule(s) → vesicle(s) → pustule(s) → umbilicated papule(s) → ulceration → scab(s) or a polymorphic picture of lesions	PCR, NGS, electron microscopy, histopathology	Scarring, bacterial superinfection, meningoencephalitis, conjunctivitis/keratitis, bronchopneumonia, osteomyelitis, arthritis, myocarditis; especially following sexual transmission: genitoanal ulceration, proctitis, penile edema, necrotizing fasciitis	Usually self-limiting within 3-4 weeks, antiviral treatment (e.g., tecovirimat, cidofovir, brincidofovir); post-exposure prophylaxis (PEP)

(Continues)

TABLE 6 (Continued)

Disease	Pathogen	Hotspots	Incubation	Clinical picture	Diagnostics*	Complications	Treatment**
Rickettsialpox	*Rickettsia akari* (by tick bite, *L. sanguineus*)	Worldwide	7–14 days	Fever, headache, myalgia, chickenpox-like rash with usually 30-40 papules → central vesicle → brown/black eschar, regional lymphadenopathy, palms and soles usually not involved	Serology, PCR	Usually benign	Usually self-limiting within 2–3 weeks, antibiotics (e.g., doxycycline)
Syphilis (venereal)/ bejel/ yaws/ pinta	*Treponema pallidum/ pallidum endemicum pertenue/ carateum*	Worldwide/ Eastern Mediterranean region and West Africa/ humid tropical forest regions in South America, Africa, Asia, and Oceania/ Mexico, Central, and South America	14–21 days (up to 3 months)	Primary stage with one or multiple painless sore(s) usually in the genito-anal-oral region (venereal) or extremities and face, local lymphadenopathy; secondary stage with polymorphic rashes, including rough, red/reddish-brown non-pruritic lesions on palms and soles, sometimes with fever, fatigue, sore throat etc.	Serology, PCR	Scarring, latent infection, reactivation and progression to neurosyphilis, cardiovascular or ocular syphilis, involvement of bones and joints, death	Antibiotics (e.g., penicillin, doxycycline, ceftriaxone)
Tanapox/Yaba-like disease	TANV/YLDV (TANV strain Davis)	Equatorial and East Africa	3–5 days	Fever, headache, backache, small number of large and firm papules/nodules, on face, neck, and/or trunk, slow progression, no pustulation, lymphadenopathy	PCR, NGS, histology	Scarring, bacterial superinfection	Usually self-limiting within 6–8 weeks
Tularemia	*Francisella tularensis*	Northern hemisphere	3–6 days	Fever, flu-like symptoms, generalized aches, vesicular rash, ulceration and eschar, lymphadenopathy	Serology, NGS, PCR	Dissemination, leading to lung abscess, pneumonia, rhabdomyolysis, renal failure, meningitis, peritonitis	Antibiotics (e.g., gentamicin, doxycycline, ciprofloxacin)
Vaccinia	VACV	South America, particularly Brazil	Approx. 5 days	Fever, fatigue, painful pustules and/or papules usually on hands, lymphadenopathy	PCR, NGS, electron microscopy, histopathology	Bacterial superinfection, pneumonia	Usually self-limiting

Abbr.: BPSV, bovine papular stomatitis virus; BPXV, buffalopox virus; CMLV, camelpox virus; CPXV, cowpox virus; EV-A, enterovirus A; HHV-1/-2, human herpesvirus 1/2; HHV-3, human herpesvirus 3; HSV, herpes simplex virus; LGV, lymphogranuloma venereum; MeV, measles morbillivirus; MOCV, molluscum contagiosum virus; NGS, Next-Generation Sequencing; ORFV, orf virus; PCPV, pseudocowpox virus; PCR, Polymerase Chain Reaction; STI, Sexually Transmitted Infection; SSPE, Subacute Sclerosing Panencephalitis; TANV, tanapox virus; VACV, vaccinia virus; VZV, varizella zoster virus; YLDV, Yaba-like disease virus

*Most usually used,

**either approved or off-label, based on evidence from the literature.

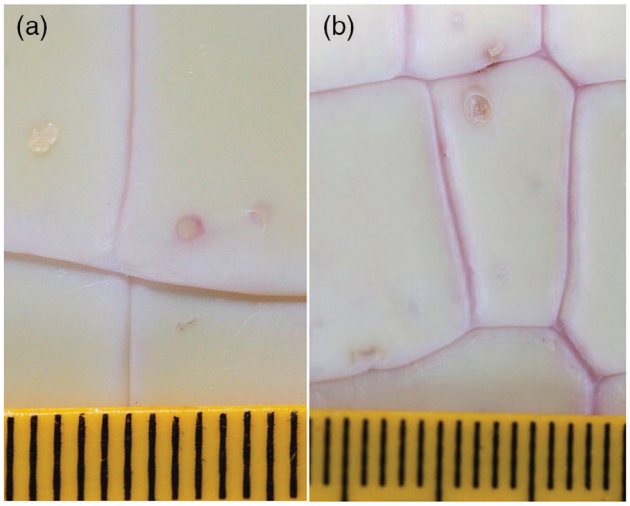

FIGURE 19 Crocodile pox on the belly skin of a juvenile saltwater crocodile (*Crocodylus porosus*). (a) Showing very early stage of active lesion, (b) after expulsion of necrotic plug (used by courtesy of S. Isberg, PhD).

candidates for the treatment of poxvirus infections are under investigation, including the tyrosine kinase inhibitor imatinib[303] and bis-benzimidazole derivatives.[304]

To reduce disease burden and optimize disease management, development of novel antivirals and vaccination strategies is key.

Interestingly, poxviruses themselves may help to advance both, therapeutics and vaccines for their unique molecular properties. Within their very large virions, poxviruses can easily harbor artificially inserted gene fragments, e.g. for vector-based vaccines as has been proposed for COVID-19.[305,306] Similarly, poxvirus particles can serve as vehicles for oncolytic virotherapy of cancer comparable to Talimogen laherparepvec (T-Vec) in the treatment of melanoma.[307]

That is, poxvirus infections "have shaped modern medicine and biomedical science".[307]

CLINICAL DECISION SUPPORT FOR THE DIFFERENTIAL DIAGNOSIS OF POXVIRUS INFECTIONS

The differential diagnosis of poxvirus infections can be challenging, requiring thorough assessment of patient history, consideration of epidemiologic information, and laboratory testing. Specific differential diagnoses include chickenpox or hand-foot-and-mouth disease, but also bacterial infections such as cutaneous anthrax or tularemia, and protozoan infections such as leishmaniasis. Table 6 provides an overview of specific infectious differential diagnoses.

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CONFLICT OF INTEREST

None.

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[CME Questions / Lernerfolgskontrolle]

1. In der Subfamilie *Chordopoxvirinae* sind aktuell 22 Genera klassifiziert. Welche Aussage trifft zu?
   a. Vertreter aller Genera können den Menschen (*Homo sapiens*) infizieren und eine Erkrankung auslösen.
   b. Seit der Pockeneradikation (Variola major/vera) sind alle Pockenvirusinfektionen Zoonosen.
   c. Alle Pockenvirusinfektionen entwickelten sich vor dem Speziesübergang auf andere Tiere entwicklungsgeschichtlich zunächst im Menschen (*Homo sapiens*).
   d. Vertreter der meisten Genera haben ihr natürliches Reservoir im Tierreich; einige können den Menschen (*Homo sapiens*) infizieren.
   e. Veränderungen in der Pockenvirus-Klassifikation wird es gemäß Konsensus des *International Committee on Taxonomy of Viruses* (ICTV) nach 2009 nicht mehr geben.

2. Üblicherweise wirken Antikörper gegen Vertreter des gleichen Genus kreuzprotektiv, das heißt:
   a. Eine vorangegangene CPXV-Infektion (Kuhpocken) kann vor Orf schützen.
   b. Eine vorangegangene ORFV-Infektion (Orf) kann vor Mpox schützen.
   c. Eine vorangegangene BPSV-Infektion (bovine papulöse Stomatitis) kann vor Vaccinia schützen.
   d. Eine vorangegangene VACV-Infektion (Vaccinia) kann vor Mpox schützen.
   e. Eine vorangegangene CMLV-Infektion (Kamelpocken) kann vor Dellwarzen schützen.

3. Welche post- oder parainfektiösen Pockenvirus-assoziierten Erkrankungen sind am häufigsten beschrieben?
   a. Akute demyelinisierende Encephalomyelitis (ADEM) und subakut sklerosierende Panencephalitis (SSPE)
   b. Fatigue und Belastungsintoleranz
   c. Erythema exsudativum multiforme (EEM) und bullöse Dermatosen, zum Beispiel bullöses Pemphigoid
   d. Glomerulonephritis, einschließlich Minimal-Change Nephropathie
   e. Reaktive Arthritis und postinfektiöser Hypothyreoidismus

4. Welche Aussage zum Nachweis von Pockenvirusinfektionen trifft am ehesten zu?
   a. Ein Abstrich (Abstrichtupfer mit Plastikstab) von Hautläsionen eignet sich für den PCR-Nachweis (Nukleinsäure-gestütztes Nachweisverfahren, NAAT) von Pockenviruserbgut.
   b. Der PCR-Nachweis von Pockenviruserbgut beweist eine ansteckungsfähige Pockenvirusinfektion.
   c. Das Nukleinsäureamplifikat (zum Beispiel aus PCR) dient zum elektronenmikroskopischen Nachweis.
   d. Aus formalinfixiertem Gewebe (FFPE) kann kein PCR-Nachweis (Nukleinsäure-gestütztes Nachweisverfahren, NAAT) von Pockenviruserbgut gelingen.
   e. Serologische Tests eignen sich für den sicheren Nachweis einer akuten Pockenvirusinfektion.

5. Im Rahmen der Pockeneradikation und darüber hinaus wurden effektive Vakzine zur Prävention von Orthopockenvirusinfektionen entwickelt. Welche Aussage trifft zu?
   a. Vakzine der ersten Generation (zum Beispiel Dryvax) stellen heute die bevorzugte Wahl dar; der Erfahrungsschatz und die Evidenz sind hier am größten.
   b. Für Schwangere, Immunkompromittierte und in Einzelfallentscheidungen kommen Vakzine der ersten Generation (zum Beispiel Dryvax) zum Einsatz.
   c. Die Inzidenz von Orf, boviner papulöser Stomatitis und Melkerknoten wurde durch konsequente Vakzinierung zur Primärprävention von Orthopockenvirusinfektionen reduziert.
   d. Es ist ungewiss, ob eine Vakzinierung aus der Zeit der Pockenviruseradikation (bis 1980) einen sicheren Immunschutz gegen Orthopockenvirusinfektionen bis heute aufrechterhält
   e. Zu den häufigsten Nebenwirkungen nach Impfung (adverse events following immunization; AEFI) mit Vakzinen der zweiten und dritten Generation zählen die Impfpocken.

6. Welche Aussage trifft zur Therapie von Mpox am ehesten zu?
   a. Die chirurgische Therapie ist immer das Mittel der ersten Wahl.
   b. Meist genügt eine symptomatische Therapie.

c. Für komplizierte klinische Verläufe sind mehrere antivirale Wirkstoffe zugelassen.
d. Aciclovir kann zur Therapie eingesetzt werden; die Dosis muss an die Nierenfunktion angepasst werden.
e. Da Mpox selten selbstlimitierend verlaufen, ist eine Therapie in der Mehrzahl der Fälle unabdingbar.

7. Welchen Aspekt sollte die Anamnese im Hinblick auf Tanapocken als tropendermatologische Differenzialdiagnose insbesondere berücksichtigen?
   a. Alter und Geschlecht der erkrankten Person
   b. Reiseziel/-verlauf, Reisezeitraum und Tierkontakte der erkrankten Person
   c. Sexualkontakte der erkrankten Person
   d. Verzehrte Nahrungsmittel, insbesondere Rohmilchprodukte
   e. Blutgruppe der erkrankten Person

8. Einige Pockenvirusinfektionen gelten als sexuell übertragbar. Welche Aussage trifft zu?
   a. Es sollte zügig eine antibiotische Postexpositionsprophylaxe gegen STI (Doxy-PEP) eingeleitet werden.
   b. Es müssen alle Kontaktpersonen der letzten 12 Monate benachrichtigt werden, wenn Dellwarzen festgestellt wurden.
   c. Patienten mit gesicherter MPXV-Infektion sollte ein vollständiges STI-Screening angeboten werden.
   d. Kondome schützen sicher vor einer Übertragung von MPXV.
   e. Personen, die eine HIV-PreP nehmen, sind aufgrund der antiviralen Therapie vor einer Ansteckung geschützt.

9. Personen, die an Mpox erkrankt sind, sollten ausführlich beraten werden und erhalten spezifische Empfehlungen von Seiten der Gesundheitsbehörden. Welche Empfehlung trifft **nicht** zu?
   a. Vermeiden Sie engen Kontakt mit anderen Menschen, insbesondere mit Säuglingen und Kleinkindern, Schwangeren oder immunsupprimierten Personen.
   b. Vermeiden Sie engen Kontakt mit Haustieren wie Hunden und Katzen, Hamstern, Kaninchen, Mäusen und Ratten.
   c. Verzichten Sie auf sexuelle Aktivitäten und engen Körperkontakt, bis der Ausschlag abgeheilt ist.
   d. Vermeiden Sie ausgiebiges Lüften, da sonst Viruspartikel in die Umwelt getragen werden.
   e. Benutzen Sie nur bestimmte Haushaltsgegenstände (Kleidung, Bettwäsche, Handtücher, Essgeschirr, Teller, Gläser), die nicht mit anderen Haushaltsmitgliedern geteilt werden sollten.

10. Welche Aussage zur Meldepflicht nach Infektionsschutzgesetz (IfSG) trifft **nicht** zu?
    a. Dem Gesundheitsamt werden gemäß § 6 Abs. 1 Nr. 1 Buchst. u IfSG der Krankheitsverdacht, die Erkrankung sowie der Tod in Bezug auf durch Orthopockenviren verursachte Krankheiten gemeldet.
    b. Dem Gesundheitsamt werden gemäß § 7 Abs. 1 Nr. 36a IfSG der direkte oder indirekte Nachweis von Orthopockenviren, soweit die Nachweise auf eine akute Infektion hinweisen, namentlich gemeldet.
    c. Das Gesundheitsamt übermittelt gemäß § 11 Abs. 1 IfSG an die zuständige Landesbehörde nur Erkrankungs- oder Todesfälle und Erregernachweise, die der Falldefinition gemäß § 11 Abs. 2 IfSG entsprechen.
    d. Die namentliche Meldung durch den feststellenden Arzt oder die Untersuchungsstelle (Laboratorien, Einrichtungen der pathologisch-anatomischen Diagnostik) hat laut § 9 Abs. 3 IfSG unverzüglich zu erfolgen und muss dem Gesundheitsamt spätestens 24 Stunden, nachdem der Meldende Kenntnis erlangt hat, vorliegen, auch wenn einzelne Informationen zur Meldung noch unvollständig vorliegen.
    e. Infektionen mit Windpocken (Varizella zoster-Virus, HHV-3) sind gemäß § 6 IfSG nicht meldepflichtig.

Liebe Leserinnen und Leser,
der Einsendeschluss an die DDA für diese Ausgabe ist der 31.März 2024.

Die richtige Lösung zum Thema "Pemphigus– und Pemphigoid-Erkrankungen: Klinik, Diagnostik und Therapie" in Heft 10/2023: 1c, 2a, 3d, 4c, 5b, 6a, 7b, 8e, 9a, 10a

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