Frontiers in Health Informatics
ISSN-Online: 2676-7104
www.healthinformaticsjournal.com
2024; Vol 13: Issue 8
Open Access

Is Cowpox Virus Infection: An Emerging Health Threat

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Cite this paper as: Anjali Singh, Aasma Kossar, Kajal Patel, Neelam Sharma, Rahul Chaurasia, Suman Bansal, Sarita Karole, Deepak Kumar Jain (2024). Is Cowpox Virus Infection: An Emerging Health Threat. *Frontiers in Health Informatics*, *13 (8) 1943-1952*

ABSTRACT

The orthopox virus is the zoonosis that causes cowpox. Edward Jenner describes it for the first time in relation to the variola virus vaccination. Despite their name, cows are not the primary source of infection; cats are more likely to get the virus by eating mice and rats that are sick. The primary hosts of the cowpox virus are house mice, short-tailed field voles, wood mice and bank voles. The incubation duration is seven to twelve days, occasionally three weeks.While the smaller peak happens in the winter (February–March), the larger peak happens in the late summer/autumn (August–October). The virus causes mucous membrane or skin infections, which lead to the development of a localized pustular skin illness. Elisa testing, real-time PCR, and several other diagnostic techniques can identify it. While there isn't a specific antiviral medication licensed to treat cowpox infections, cidofovir can be used in more complex instances. It may be important to have plastic surgery to prevent significant cosmetic repercussions. This review paper examines cowpox, focusing on its epidemiology and treatment.

Key words: Orthopoxvirus, Cowpox, Zoonosis, Variola Virus

INTRODUCTION

Cowpox virus (CPXV) belongs to the family Poxviridae and genus Orthopoxvirus (OPV). It has close kinship with other human-pathogenic OPV species, including vaccinia virus, variola virus, and monkeypox virus. A growing incidence of human illnesses contracted by contact with cats or other zoo animals has been reported. CPXV infection is a zoonosis similar to vaccinia and monkeypox virus [1-4].Europe has a close variation of VACV called CPXV. When Edward Jenner characterized the effectiveness of CPXV scarification in generating protective immunity against variola virus challenge, he was referring to CPXV as the source of the first vaccine. Jenner's explanation of vaccination was the first scientific one [5-6].Smallpox's causal agent, variola virus (VARV), is one of the viruses identified from animals that is included in the cowpox virus (CPXV) [7].In most cases, human cowpox is an uncommon zoonotic illness that resolves on its own. However, it can worsen and even kill people who are immunocompromised, have atopic dermatitis or Darier's disease, are undergoing steroid therapy, or have eczema, especially in youngsters [8-11]. While human cowpox is a

zoonosis, cows are not frequently afflicted, despite the name. The domestic cat is the most often identified cause of human infection, and the virus is most likely sustained in populations of wild rodents [12].The virus is implanted into damaged skin to cause cowpox[1].The biggest genome (224–228 kbp) is found in CPXV [13-14].

HISTORY AND EPIDEMIOLOGY

The evolutionary history of CPXV remains unknown, however some researchers believe that the disease was first documented in medicine in 1798/99 with Edward Jenner's publications "Inquiry" and "Further observations on the VariolaeVaccinae," in which he proved that scarification of the cowpox virus (also known as "true cowpox" or "variolaevaccinae") could prevent variola virus (VARV) infections [15]. The virus known as cowpox virus (CPXV) is named for the pustular lesions that it causes on milking cows' teats. Before the early 1970s, it was thought that cowpox exclusively affected cattle by enzootic transmission.Contrary to its name, it has been suggested by DERRICK BAXBY that cowpox does not naturally occur in cows due to enzootic in cattle[16].There has never been any evidence of CPXV spreading from person to person.Direct contact with infected cats can result in the transmission of CPXV to humans [17].Cats are probably infected by feeding on mice and rats carrying the virus [16-17].It is believed that CPXV is mostly found in wild rats [18-19]. A rising number of cases of CPXV infections have been reported in both domestic (cats, dogs, and horses) and zoo (e.g., elephants, rhinoceroses, okapis, lions, cheetahs, anteaters, and monkeys) animals [20-25].Humans can get zoonotic viruses by coming into close contact with infected animals, although cases are rare [24]. Humans and domestic and zoo animals may have unintentionally become hosts of CPXV due to infections that spread from reservoir hosts [26].Russia and England are the original countries to report cases of CPXV infections[27].In 1985, news from the Netherlands revealed the first documented case of CPXV being spread by a cat to a man [28]. The cowpox virus is currently present in portions of northern and central Asia, Europe, Turkmenistan, Israel, and maybe Egypt [29-30]. Western Eurasia IS home to the endemic cowpox virus [24, 31].Studies on the epidemiology of CPXV infection in cats and zoo animals show that there are seasonal peaks all year long. The largest peak occurs in late summer/autumn (August–October) while the lesser one occurs in winter (February–March). The majority of cats are believed to get the disease from hunting wild rodents, whereas elephants and other herbivores are believed to contract the disease by consuming grass, hay, or straw tainted with rodent faeces or urine carrying CPXV [32-38].

THE CASES

A 19-year-old female veterinary student, who had previously been healthy and constantly socialized with numerous animal varieties, developed a little red plaque on her left cheek. The lesion developed over the course of the next three weeks into a 4 cm ulcerated nodule with a satellite papule, a brownish eschar on top, and considerable skin atrophy surrounding it [39].This 24-year-old male presented with lethargy, three hemorrhagic partly ulcerated nodules in his right groyne, and surrounding oedema and inflammation that had developed over the course of a week. On his left knee, left ankle, and right shoulder, he exhibited the same isolated skin lesions. Upon examination, he showed painful widespread lymphadenopathy and a fever (38.5°C)[40]. His cat went away after developing ulcerating nodules in the 32-year-old renal transplant patient. He had many scratches from his cat, which resulted in the development of flu-like symptoms and a quickly progressing skin sore on his right hand. A skin sample and real-time PCR were used to confirm the diagnosis of cowpox (CPXV) infection [GPXV infection in an immune compromised patient] [41]. A 43-year-old man arrived with a fluctuant, nontender, single, hemorrhagic bulla measuring 25 9 20 mm. Additionally, there was central necrosis on the left volar wrist, left arm edoema that appeared on days 2, 4, and 8, lymphangitis, and a 38 5 °C fever. His cat had gotten ill recently and had acquired a number of degraded and erythematous annular lesions, measuring 3-5 mm [42].a female of eighteen. While visiting a friend who owned numerous domestic rats, she was scratched on her right arm by one of the pet rats (Rattus norvegicus). At the end of December 2008, one rat had been bought from a pet store. Four days after purchasing, the rat had epistaxis, junctivalhaemorrhages, and sneezing fits. The patient sought care at Compiègne Hospital's emergency room on January 4, 2009 [43].54 instances of human cowpox that had been reported from all across Europe during the preceding fifteen years were evaluated by Baxby et al. in 1994[1].

VIROLOGY

CPXV, also known as the genus orthopoxvirus in the family Poxviridae, is a DNA virus related to the smallpox and monkeypox viruses and somewhat similar to the vaccinia virus genetically and antigenically, albeit not exactly the same[44, 45].The orthopoxvirus genus includes the viruses that cause cowpox and monkeypox, which have a rodent reservoir, as well as the viruses that cause smallpox and vaccinia virus, which are only infections that affect humans. Unlike the ovoid parapoxvirus genus, these are huge, brick-shaped viruses with a DNA genome in a dumbbell-shaped core that replicates in the cytoplasm. these are comparable to the yatapoxvirusgenus and the molluscipox viruscontained around 215 and 219 open coding structures, their genomes, which varied in size from 220 to 222 kbp. In accordance to the results of the phylogenetic study of 87 orthopoxvirus varieties, which comprised the Fennoscandian CPXV isolates tested, the CPXV types can be further separated into 18 sub-species based on inherited and patristic distances. These strains can be divided into at least 5 distinct major clusters, which include, two, CPXV-like 1, VARV-like, VACV-like,CPXV-like 2,and ECTV-Abatino-like. Using concatenation 62 non-recombinant invariant genes of 55 CPXV, a Bayesian time-scaled history of evolution of CPXV has been established. A forecast of 1.65 parts per million × 10−5 substitution/site/year for the CPXV evolution rate was determined[46-48].Large eosinophilic A-type inclusion (ATI) bodies in the cytoplasm and the development of 2-4 mm flattened, fairly rounded pocks with a red central hemorrhagic area on the chorioallantoic membrane of embryonated eggs at 72 hours after infection are the two characteristics that set CPXV apart from other OPV species.The genomes of numerous pox viruses, notably the three different CPXV strains Germany-91 (Ger91), GRI-90 (GRI), and Brighton Red (BR), have been sequenced [49].Although CPXV has been identified as a single species, it has been suggested that CPXV really belongs to a polyphyletic group [50-54]. CPXV has been classified into a minimum of five clades by phylogenetic analyses. VACV-like, VARV-like, ECTV-Abatino-like, CPXV-like 1, and CPXV-like 2 [55].

TRANSMISSION OF THE COWPOX VIRUS AND PATHOGENESIS

Since CPXV is enzootic in cattle, it is an uncommon occupational infection. Wild rodents are the virus's natural reservoir, with bank voles having the greatest seroprevalence ever documented. (Clethrionomysglareolus).Animal hosts in Europe and Great Britain include Norway lemmings (Lemmuslemmus), bank voles (C. glareolus), wood mice (Apodemussylvaticus), short-tailed field voles (Microtus agrestis) and house mice (Mus musculus)[56-59].

HOST IMMUNE CHANGES BYCOWPOX VIRUS

Modulation of the host immune response by cowpox virus: The virus enters the body through skin or mucous membrane infections, resulting in the development of a localized pustular skin infection, frequently on the hands. The location of the lesions elsewhere, such as on the face, neck, or feet, may be determined by scratches or abrasions on the skin brought on by an infected rural cat or animal.The lymph nodules that drain enlarge, and there may occasionally be subsequent lesions. Poisons typically recover in 3-5 weeks, however bacterial superinfections can cause illnesses to last up to 8 weeks[60].Certain incidences of necrotic conjunctivitis have been documented [1].The incubation period lasts between seven and twelve days, with rare increases to three weeks [61, 62].With an average genome size of about 220 kbp, which is roughly 30 kbp bigger than the VACV genome, CPXV is the biggest poxvirus. It is able to replicate in the cytoplasm and encodes its own DNA replication and transcription machinery, eliminating the possibility of integration into the host genome. Similar to VACV, CPXV develops in vitro in monkey cells[63]. Because of their sequence similarity to cellular immunity proteins, several viral proteins have been implicated in immune response modulation[64].According to some theories, CPXV is the oldest and most similar to the common ancestor virus since it has the biggest genome, which includes numerous ORFs shared by other OPXV in addition to some unique ORFs.The immune evasion proteins that CPXV encodes are highly numerous and jointly target a broad spectrum of anti-viral host responses[88].

Complement evasion: Upon encountering an invasive pathogen, the innate immune system's initial response is complementing activation. Utilizing a sophisticated series of proteolytic cleavages of over thirty plasma and cell

membrane proteins, the complement system triggers an inflammatory response, phagocyte and neutrophil chemotaxis, neutralisation of the pathogen and subsequent opsonization, and destruction of the infected cells [89, 90].Poxviruses, like other enveloped viruses, evade complement system activation by using host complement regulatory proteins [91-93].Inflammation modulatory protein (IMP), the complement regulatory protein of CPXV, bears a striking resemblance to its orthologs in OPXV. It has been demonstrated that these proteins bind to C3 and C4 and function as a cofactor for factor I, a host complement control protein that cleaves and inactivates C3b and C4b, to block both conventional and alternative pathways [64].

Inhibition of TNF-induced responses:CPXV and other OPXV block TNF-mediated reactions at multiple points in time: they stop NFkB activation to stop TNF from being expressed in the first place; they obstruct TNF and LT-a to stop TNF-signal transduction; and they block caspase-8 and granzyme B to stop the induction of apoptosis in infected cells [64]. A shared homolog of VACV K1L to all OPXV and the pathogenic OPXV-expressed CP77 and CPXV 006 are the three NFkB-inhibiting proteins that CPXV encodes[94]. VACV and kindred poxviruses were also shown to have CPXV cytokine response modifier A (CrmA), the first poxviral caspase inhibitor identified [95].Serpins, also known as SPI, are a subfamily of serine protease inhibitors, and CrmA proteins are believed to function as suicide substrates. CPHXV In comparison to its orthologs, CrmA is the most powerful inhibitor. It effectively inhibits both granzyme B and caspase-8, protecting infected cells against TNF-induced apoptosis and T-cell-mediated cytotoxicity. Further evidence that CrmA is involved in the downregulation of cytokine signalling comes from the observation that it inhibits caspase-1, which is necessary for the proteolytic maturation of IL-1b and IL-18 [64].

Blockade of interferon response: To combat the interferon response, CPXV and other OPXVs employ a variety of tactics. To stop the interferon response from starting, they sequester d RNA, obstruct PKR signaling, express decoy receptors for type I and II IFNs, and produce the interferon-induced cytokines IL-18 and IL-1b [64-65].

Suppression of cytokine signaling: Though they have nothing in common with the cellular receptor, CPXV and ECTV have been shown to selectively bind to IL-1b, inhibiting its interaction with the receptor and halting the growth of B- and T-cells. A specific subfamily of D. Alzhanova, K. Fru¨h / Microbes and Infection 12 (2010) 900e909 905 chemokines, CC-chemokines that have been demonstrated to attract macrophages and T-cells, is selectively bound to and suppressed by viral chemokine inhibitor (vCCI), which is produced by all OPXVs [64].

Inhibition of NK cell activation: The protein known as OPXV MHC I-like protein (OMCP) is secreted and is encoded by CPXV and MPXV. The OMCP protein was also demonstrated to bind to mouse and human NKG2D receptors with a high degree of affinity.According to Campbell (2007), OMPC decreased NK cell-mediated cytotoxicity by competitively blocking NKG2D's interaction with cellular ligands. CPXV and MPXV's production of an NKG2D inhibitory ligand appears to be a less selective and more beneficial tactic than herpesviruses' downregulation of cellular NKG2D ligands, given that NKG2D is crucial for the activation of both NK and T-cells. The immunoglobulin receptor translocation associated protein 2 (IRTA2), also known as FcR-like 5 (FCRL5), is a novel cellular receptor for OMPC that has been recently identified [66].

T-cell evasion by downregulation of MHC I expression: The expression of MHC I on the cell surface is impeded by CPXV infection, and this is identically related with the attenuation of CD8þ T-cell activation by the infected Ag-presenting cells [67]. CPXV has evolved mechanisms involving two distinct ORFs (Open Reading Frames), 203 and BR-012, to interfere with MHC I expression in both mouse and human hosts [68, 69].The regulation of intracellular infections, especially viral infection, is significantly aided by CD8ξ T-cell-mediated responses. When a T-cell receptor identifies an antigen (Ag)-derived peptide presented by MHC I, T-cells that have scanned MHC I complexes on the cell surface get activated.

Otherimmunomodulating proteins: More CPXV-encoded proteins with potential immunomodulatory roles that are still unknown include orthologs of VACV growth factor (VGF), a secreted homolog of epidermal growth factor that stimulates cell proliferation in quiescent states necessary for effective virus replication; 3b-hydroxysteroid

dehydrogenase, a steroid hormone and virulence factor; and a homolog of semaphorins, a homolog of cellular regulatory proteins that are likely to be involved in mediating an inflammatory response[70].

HISTOPATHOLOGY

According to the specimens under investigation, the epidermis had extensive intracellular and intercellular edema and intense dermal polymorphnuclear leukocytic infiltration encroaching on the epithelium [71].Full-thickness necrosis of the skin was shown by histopathology. Electron microscopy identified brick-shaped orthopoxvirus particles, and a quantitative real-time PCR test for the cowpox virus's haemagglutinin gene yielded a positive result, confirming the diagnosis of human cowpox. Direct DNA sequencing was used to determine the identity of the strain AT_Styria/84/09 (Genbank accession number FJ7692784) by sequence analysis. The specimen is closely linked to a cowpox virus that was isolated from domestic cats in Austria [39].

DIAGNOSIS

Real-time PCR and skin biopsies verified the diagnosis of cowpox (CPXV) infection.[41]An antigen-capture ELISA, a competition test, or a plaque reduction test can be used to identify OPV-specific antibodies in sera[60]. It is necessary to evaluate positive serological results whileconsideringprior smallpox immunizations. Histological sections of cutaneous specimens have been utilized to retrospectively diagnose CPXV infections by the usage of ATI bodies[72]. One of the most frequently produced late proteins, measuring 160 kDa, makes up ATI bodies together with additional components (such structural protein P4c) that promote the incorporation of mature virions [73].Conventional methods for identifying CPXV in bioptates or swabs include electron microscopy and propagation on suitable cell cultures. For the purpose of differentiating OPVs to the species or strain level, PCR assays that target various genes (such as the hemagglutinin gene, ATI gene, crmB gene, random amplified polymorphic DNA analysis (RAPD) of genomic DNA, Southern blot and dot-blot assays) have been utilized [74-79].

TREATMENT AND PREVENTION

Local and systemic treatment schemes are used to avoid bacterial hyperinfection of the skin lesions, especially in immunocompromised individuals and those with a history of eczema, as there is currently no formal therapy for this condition[80]. In several instances, lesions were surgically removed as a result of delayed diagnosis[81-83].Nonetheless, one clinical instance of cowpox was documented with the off-label use of cidofovir.When consequences from the cowpox infection are evident, cidofovir, a nucleotide analogue with significant side effects, is given. It has been effectively studied in vitro[84]. Viral egress from infected cells is inhibited by ST-246, an oral medication.Novel candidates for illness treatment include the new agent ST-247[85, 86].After receiving intravenous therapy for two weeks with a combination of piperacillin and tazobactam together with clindamycin and doxycycline, the nodule became visible but continued, necessitating a full necrectomy[39]. Chlorhexidine washings, fusidic acid-containing wound dressings, intravenous dicloxacillin, and isolation rooms are advised, especially for eczematic patients[8]. Amoxicillin and clavulanic acid were used orally to treat the staphylococcal superinfection. Within a week, the surrounding erythema went away, and the CRP level dropped to 7.6 mg/l, although some fluid continued to leak from the ulcer[3]. The FDA-approved drug mitoxantrone was previously found to exhibit antiviral action against the vaccinia virus. Mitoxantrone is used to treat cancer and multiple sclerosis. Mitoxantrone's EC50 values against cowpox and monkeypox were 0.25 lM and 0.8 lM, correspondingly. The survival rate and duration of C57Bl/6 mice infected with the cowpox virus improved to 25% and substantially when they received 0.5 mg/kg of mitoxantrone intraperitoneally. In vitro tests demonstrated a substantial simultaneous effect of both drugs on cowpox, but not on animal survival or the median time to death in BALB/c mice infected by the nose. Significantly fewer mice survived when given 100 mg/kg of cidofovir alone as opposed to 0.5 mg/kg of mitoxantrone[87]. Plastic surgery may be required to prevent significant aesthetic repercussions.

FUTURE PROSPECTIVE AND CONCLUSION

Cowpox is an emerging human zoonotic hazard that raises concerns for public health as well as the development and introduction of an effective vaccine and antiviral agent. These concerns are prompted by the growing number of reports

of human cowpox infection, the expanding animal host range, the decline in immunity, and the limited availability of antiviral agents.

In summary, the current investigation has shown that CPXV is polyphyletic and that isolates from it exhibit a significant degree of genetic variation. Moreover, our results verified that CPXV was a polyphyletic collection of many species rather than a single species. In order to completely remove this fatal illness and prevent its recurrence in the future, several actions must be followed. Public knowledge of the disease's epidemiology and transmission is essential for this goal. The diagnosis of cowpox infection can be made by isolation and identification, which calls for the use of biosafety protocols, serological tests such as ELISA, electron microscopy, and nucleic acid detection techniques like as RT-PCR and real-time RT-PCR. The gaps in the study, including the range and frequency of results in All of these will eventually aid in the development of novel vector control products, highly effective medicines, and potent vaccinations for human protection. Under these circumstances, we must act quickly.

REFERENCES

1. Baxby D, Bennett M, Getty B. Human cowpox 1969–93: a review based on 54 cases. British Journal of Dermatology. 1994; 131(5):598-607.
2. Wolfs TF, Wagenaar JA, Niesters HG, Osterhaus AD. Rat-to-human transmission of cowpox infection. Emerging infectious diseases. 2002; 8(12):1495.
3. Hemmer CJ, Littmann M, Löbermann M, Meyer H, Petschaelis A, Reisinger EC. Human cowpox virus infection acquired from a circus elephant in Germany. International journal of infectious diseases. 2010; 14:e338-40.
4. Lawn R. Risk of cowpox to small animal practitioners. The Veterinary Record. 2010;166(20):631.
5. Jenner E. The Three Original Publications on Vaccination Against Smallpox. Vol. XXXVIII, Part 4. The Harvard Classics. New York: PF Collier & Son, 1909–14; Bartleby. com, 2001.
6. Carroll DS, Emerson GL, Li Y, Sammons S, Olson V, Frace M, Nakazawa Y, Czerny CP, Tryland M, Kolodziejek J, Nowotny N. Chasing Jenner's vaccine: revisiting cowpox virus classification. PloS one. 2011; 6(8):e23086.
7. Alzhanova D, Früh K. Modulation of the host immune response by cowpox virus. Microbes and Infection. 2010; 12(12-13):900-9.
8. Pelkonen PM, Tarvainen K, Hynninen A, Kallio ER, Henttonen H, Palva A, Vaheri A, Vapalahti O. Cowpox with severe generalized eruption, Finland. Emerging infectious diseases. 2003;9 (11):1458.
9. Czerny CP, Eis-Hübinger AM, Mayr A, Schneweis KE, Pfeiff B. Animal poxviruses transmitted from cat to man: current event with lethal end. Journal of Veterinary Medicine, Series B. 1991; 38(1-10):421-31.
10. Haase O, Moser A, Rose C, Kurth A, Zillikens D, Schmidt E. Generalized cowpox infection in a patient with Darier disease. British Journal of Dermatology. 2011; 164 (5):1116-8.
11. Eis-HübingerAM, Gerritzen A, Schneweis KE. Fatal cowpox-like virus infection transmitted by cat. Fatal cowpox-like virus infection transmitted by cat.Lancet, 1990, 336 (6):880.
12. Crouch AC, Baxby D, McCracken CM, Gaskell RM, Bennett M. Serological evidence for the reservoir hosts of cowpox virus in British wildlife. Epidemiology & Infection. 1995; 115(1):185-91.
13. Esposito JJ, Knight JC. Orthopoxvirus DNA: a comparison of restriction profiles and maps. Virology. 1985;143(1):230-51.
14. Essbauer S, Meyer H. Genus orthopoxvirus: Cowpox virus. Poxviruses. 2007:75-88.
15. Baxby D. Jenner's smallpox vaccine: the riddle of vaccinia virus and its origin. 1981.
16. Baxby D, Bennett M. Cowpox: a re-evaluation of the risks of human cowpox based on new epidemiological information. Springer Vienna; 1997.
17. Coras B, Eßbauer S, Pfeffer M, Meyer H, Schröder J, Stolz W, Landthaler M, Vogt T. Cowpox and a cat. The Lancet. 2005;365(9457):446.

18. Bennett M, Crouch AJ, Begon M, Duffy B, Feore S, Gaskell RM, Kelly DF, McCracken CM, Vicary L, Baxby D. Cowpox in British voles and mice. Journal of Comparative Pathology. 1997;116(1):35-44.
19. Kinnunen PM, Henttonen H, Hoffmann B, Kallio ER, Korthase C, Laakkonen J, Niemimaa J, Palva A, Schlegel M, Ali HS, Suominen P. Orthopox virus infections in Eurasian wild rodents. Vector-Borne and Zoonotic Diseases. 2011;11(8):1133-40.
20. Bennett M, Gaskell CJ, Baxbyt D, Gaskell RM, Kelly DF, Naidoot J. Feline cowpox virus infection. Journal of Small Animal Practice. 1990;31(4):167-73.
21. Jäger K, Steinborn P, Weider K, Wohlsein P. Kutane Infektion mit Orthopoxvirus bovis bei einem Wachtelhund. Tierärztliche Praxis Ausgabe K: Kleintiere/Heimtiere. 2016; 44(04):273-7.
22. Pfeffer M, Burck G, Meyer H. Kuhpockenviren in deutschland: Eine analyse von 5 Fällenaus dem Jahr 1998. Berl Munch TierarztlWochenschr. 1999; 112:334-8.
23. Scarff D. Cowpox (orthopox virus) in the cat. UK Vet Companion Animal. 2012;17(4):36-8.
24. Essbauer S, Pfeffer M, Meyer H. Zoonotic poxviruses. Veterinary Microbiology. 2010; 140(3-4):229-36.
25. Pilaski J, Jacoby F. Die Kuhpocken-Erkrankungen der Zootiere. Verh berErkrgZootiere. 1993; 35:39-50.
26. Hoffmann D, Franke A, Jenckel M, Tamošiūnaitė A, Schluckebier J, Granzow H, Hoffmann B, Fischer S, Ulrich RG, Höper D, Goller K. Out of the reservoir: phenotypic and genotypic characterization of a novel cowpox virus isolated from a common vole. Journal of Virology. 2015;89(21):10959-69.
27. Marennikova SS, Maltseva NN, Korneeva VI, Garanina NM. Outbreak of pox disease among carnivora (felidae) and edentata. Journal of Infectious Diseases. 1977;135(3):358-66.
28. Willemse A, Egberink HF. Transmission of cowpox virus infection from domestic cat to man. Lancet. 1985;1(8444).
29. Pauli G. Infektionen mit Kuhpockenviren in Deutschlandeine Ubersicht (Infections with cowpox viruses in Germany an overview). Epidemiol Bull. 2007; 10:1-3.
30. Laakkonen J, Kallio-Kokko H, Öktem MA, Blasdell K, Plyusnina A, Niemimaa J, Karataş A, Plyusnin A, Vaheri A, Henttonen H. Serological survey for viral pathogens in Turkish rodents. Journal of Wildlife Diseases. 2006;42(3):672-6.
31. Franke A, Pfaff F, Jenckel M, Hoffmann B, Höper D, Antwerpen M, Meyer H, Beer M, Hoffmann D. Classification of cowpox viruses into several distinct clades and identification of a novel lineage. Viruses. 2017;9(6):142.
32. Franke A, Kershaw O, Jenckel M, König L, Beer M, Hoffmann B, Hoffmann D. Fatal cowpox virus infection in an aborted foal. Vector-Borne and Zoonotic Diseases. 2016 ;16(6):431-3.
33. Pilaski J, Von Witzendorff P, Brandt HP, HOHR D. Ein Pockenausbruch bei Elefanten (Elephas maximus, Loxodonta africana) in einem Wanderzirkus während des Aufenthaltes im Winterquartier, Verhandlungsbericht des 37. InInternationalen Symposiums über die Erkrankungen der Zoo-und Wildtiere 1995; 24(28): 357-363.
34. Appl C, Von Bomhard W, Hanczaruk M, Meyer H, Bettenay S, Mueller R. Feline cowpoxvirus infections in Germany: clinical and epidemiological aspects. Berliner MünchenerTierärztlicheWochenschrift. 2013;126:55-61.
35. Bennett M, Gaskell CJ, Gaskell RM, Baxby D, Gruffydd-Jones TJ. Poxvirus infection in the domestic cat: some clinical and epidemiological observations. The Veterinary Record. 1986; 118(14):387-90.
36. Pfeffer M, Pfleghaar S, Von Bomhard D, Kaaden OR, Meyer H. investigation of feline cowpox in Germany. The Veterinary record. 2002; 150:50-1.
37. Essbauer S, Hartnack S, Misztela K, Kießling-Tsalos J, Bäumler W, Pfeffer M. Patterns of orthopox virus wild rodent hosts in South Germany. Vector-Borne and Zoonotic Diseases. 2009; 9(3):301-11.
38. Hazel SM, Bennett M, Chantrey J, Bown K, Cavanagh R, Jones TR, Baxby D, Begon M. A longitudinal study of an endemic disease in its wildlife reservoir: cowpox and wild rodents. Epidemiology & Infection. 2000;124(3):551-62.
39. Glatz M, Richter S, Ginter-Hanselmayer G, Aberer W, Müllegger RR. Human cowpox in a veterinary student. The Lancet Infectious Diseases. 2010;10(4):288.

40. Grönemeyer LL, Baltzer A, Broekaert S, Schrick L, Möller L, Nitsche A, Mössner R, Schön MP, Buhl T. Generalised cowpox virus infection. The Lancet. 2017; 390(10104):1769.
41. Wendt R, Tittelbach J, Schrick L, Kellner N, Kalbitz S, Ruehe B, Michel J, Schliemann S, Elsner P, Lübbert C, Nitsche A. Generalized cowpox virus infection in an immunosuppressed patient. International Journal of Infectious Diseases. 2021; 106:276-8.
42. Haddadeen C, Van Ouwerkerk M, Vicek T, Fityan A. A case of cowpox virus infection in the UK occurring in a domestic cat and transmitted to the adult male owner. British Journal of Dermatology. 2020;183(6):e190-.
43. Ninove L, Domart Y, Vervel C, Voinot C, Salez N, Raoult D, Meyer H, Capek I, Zandotti C, Charrel RN. Cowpox virus transmission from pet rats to humans, France. Emerging Infectious Diseases. 2009;15(5):781.
44. Amer M, El-Gharib I, Rashed A, Farag F, Emara M. Human cowpox infection in Sharkia Governorate, Egypt. International Journal of Dermatology. 2001; 40(1):14-7.
45. Vorou RM, Papavassiliou VG, Pierroutsakos IN. Cowpox virus infection: an emerging health threat. Current Opinion in Infectious Diseases. 2008;21(2):153-6.
46. Moss B. Poxviridae: the viruses and their replication (2001): 1249-1283.
47. Damon IK, Esposito JJ. Poxviruses that infect humans. Manual of clinical microbiology. Washington: American Society for Microbiology. 2003:1583-91.
48. Diaz-Cánova D, Moens UL, Brinkmann A, Nitsche A, Okeke MI. Genomic sequencing and analysis of a novel human cowpox virus with mosaic sequences from North America and old world orthopoxvirus. Frontiers in Microbiology. 2022; 13:868887.
49. Lefkowitz EJ, Upton C, Changayil SS, Buck C, Traktman P, Buller RM. Poxvirus Bioinformatics Resource Center: a comprehensive Poxviridae informational and analytical resource. Nucleic acids research. 2005; 33(1):D311-6.
50. Hansen H, Okeke MI, Nilssen Ø, Traavik T. Comparison and phylogenetic analysis of cowpox viruses isolated from cats and humans in Fennoscandia. Archives of Virology. 2009;154:1293-302.
51. Okeke MI, Okoli AS, Nilssen Ø, Moens U, Tryland M, Bøhn T, Traavik T. Molecular characterization and phylogenetics of Fennoscandian cowpox virus isolates based on the p4c and atip genes. Virology Journal. 2014;11:1-6.
52. Dabrowski PW, Radonić A, Kurth A, Nitsche A. Genome-wide comparison of cowpox viruses reveals a new clade related to Variola virus. PloS One. 2013;8(12):e79953.
53. Mauldin MR, Antwerpen M, Emerson GL, Li Y, Zoeller G, Carroll DS, Meyer H. Cowpox virus: What's in a Name?. Viruses. 2017;9(5):101.
54. Babkin IV, Babkina IN, Tikunova NV. An update of orthopoxvirus molecular evolution. Viruses. 2022;14(2):388.
55. Senkevich TG, Yutin N, Wolf YI, Koonin EV, Moss B. Ancient gene capture and recent gene loss shape the evolution of orthopoxvirus-host interaction genes. MBio. 2021;12(4):10-128.
56. Chantrey J, Meyer H, Baxby D, Begon M, Bown KJ, Hazel SM, Jones T, Montgomery WI, Bennett M. Cowpox: reservoir hosts and geographic range. Epidemiology & Infection. 1999;122 (3):455-60.
57. Yeruham I, Nyska A, Abraham A, Algazi R. Occurrence of cowpox-like lesions in cattle in Israel. Revue d'élevage et de médecinevétérinaire des pays tropicaux. 1996 ;49 (4):299-302.
58. Gibbs EP, Johnson RH, Collings DF. Cowpox in a dairy herd in the United Kingdom. Veterinary Record. 1973;92(3):56-64.
59. Sandvik T, Tryland M, Hansen H, Mehl R, Moens U, Olsvik Ø, Traavik T. Naturally occurring orthopoxviruses: potential for recombination with vaccine vectors. Journal of Clinical Microbiology. 1998;36(9):2542-7.
60. Essbauer S, Meyer H, Kaaden OR, Pfeffer M. Recent cases in the german poxvirus consulting laboratory 2002: 635-642.
61. Nitsche A, Pauli G. Sporadic human cases of cowpox in Germany. Weekly releases (1997–2007). 2007;12(16):3178.

62. Wolfs TF, Wagenaar JA, Niesters HG, Osterhaus AD. Rat-to-human transmission of cowpox infection. Emerging infectious diseases. 2002;8(12):1495.
63. Ricordel M, Foloppe J, Pichon C, Sfrontato N, Antoine D, Tosch C, Cochin S, Cordier P, Quemeneur E, Camus-Bouclainville C, Bertagnoli S. Cowpox virus: a new and armed oncolytic poxvirus. Molecular Therapy-Oncolytics. 2017; 7:1-1.
64. Seet BT, Johnston JB, Brunetti CR, Barrett JW, Everett H, Cameron C, Sypula J, Nazarian SH, Lucas A, McFadden G. Poxviruses and immune evasion. Annual Review of Immunology. 2003 Apr;21(1):377-423.
65. Delaloye J, Roger T, Steiner-Tardivel QG, Le Roy D, Knaup Reymond M, Akira S, Petrilli V, Gomez CE, Perdiguero B, Tschopp J, Pantaleo G. Innate immune sensing of modified vaccinia virus Ankara (MVA) is mediated by TLR2-TLR6, MDA-5 and the NALP3 inflammasome. PLoS pathogens. 2009;5(6):e1000480.
66. Campbell JA, Davis RS, Lilly LM, Fremont DH, French AR, Carayannopoulos LN. Cutting edge: FcR-like 5 on innate B cells is targeted by a poxvirus MHC class I-like immunoevasin. The Journal of Immunology. 2010; 185(1):28-32.
67. Dasgupta A, Hammarlund E, Slifka MK, Fruh K. Cowpox virus evades CTL recognition and inhibits the intracellular transport of MHC class I molecules. The Journal of Immunology. 2007; 178(3):1654-61.
68. Byun M, Verweij MC, Pickup DJ, Wiertz EJ, Hansen TH, Yokoyama WM. Two mechanistically distinct immune evasion proteins of cowpox virus combine to avoid antiviral CD8 T cells. Cell Host & Microbe. 2009;6(5):422-32.
69. Alzhanova D, Edwards DM, Hammarlund E, Scholz IG, Horst D, Wagner MJ, Upton C, Wiertz EJ, Slifka MK, Früh K. Cowpox virus inhibits the transporter associated with antigen processing to evade T cell recognition. Cell Host & Microbe. 2009;6(5):433-45.
70. Da Fonseca FV, Alves Silva RL, Marques JO, Peregrino Ferreira PC, Kroon EG. The genome of cowpox virus contains a gene related to those encoding the epidermal growth factor, transforming growth factor alpha and vaccinia growth factor. Virus Genes. 1999;18:151-60.
71. Amer M, El-Gharib I, Rashed A, Farag F, Emara M. Human cowpox infection in Sharkia Governorate, Egypt. International Journal of Dermatology. 2001;40(1):14-7.
72. Godfrey DR, Blundell CJ, Essbauer S, Pfeffer M, Shearer DH, Rest JR, Baker JF. Unusual presentations of cowpox infection in cats. Journal of Small Animal Practice. 2004;45(4):202-5.
73. Fenner F, Wittek R, Dumbell KR. The pathogenesis, pathology, and immunology of orthopoxvirus infections. The Orthopoxviruses. 1989:85-141.
74. Ropp SL, Jin QI, Knight JC, Massung RF, Esposito JJ. PCR strategy for identification and differentiation of small pox and other orthopoxviruses. Journal of Clinical Microbiology. 1995;33(8):2069-76.
75. Meyer H, Osterrieder N, Pfeffer M. Differentiation of species of the genus Orthopoxvirus in a dot blot assay using digoxigenin-labeled DNA-probes. Veterinary Microbiology. 1993;34(4):333-44.
76. Meyer H, Ropp SL, Esposito JJ. Gene for A-type inclusion body protein is useful for a polymerase chain reaction assay to differentiate orthopoxviruses. Journal of Virological Methods. 1997; 64(2):217-21.
77. Meyer H, Schay C, Mahnel H, Pfeffer M. Characterization of orthopoxviruses isolated from man and animals in Germany. Archives of Virology. 1999; 144:491-501.
78. Loparev VN, Massung RF, Esposito JJ, Meyer H. Detection and differentiation of old world orthopoxviruses: restriction fragment length polymorphism of the crmB gene region. Journal of Clinical Microbiology. 2001;39(1):94-100.
79. Stemmler M, Neubauer H, Meyer H. Comparison of closely related orthopoxvirus isolates by random amplified polymorphic DNA and restriction fragment length polymorphism analysis. Journal of Veterinary Medicine, Series B. 2001; 48(9):647-54.
80. Nitsche A, Pauli G. Sporadic human cases of cowpox in Germany. Weekly releases (1997–2007). 2007; 12(16):3178.

81. Campe H, Zimmermann P, Glos K, Bayer M, Bergemann H, Dreweck C, Graf P, Weber BK, Meyer H, Büttner M, Busch U. Cowpox virus transmission from pet rats to humans, Germany. Emerging Infectious Diseases. 2009;15(5):777.
82. Vogel S, Sárdy M, Glos K, Korting HC, Ruzicka T, Wollenberg A. The Munich outbreak of cutaneous cowpox infection: transmission by infected pet rats. Acta Dermato-Venereologica. 2012;92(2):126-31.
83. Becker C, Kurth A, Hessler F, Kramp H, Gokel M, Hoffmann R, Kuczka A, Nitsche A. Cowpox virus infection in pet rat owners: not always immediately recognized. DeutschesÄrzteblatt International. 2009; 106(19):329.
84. De Clercq E, Neyts J. Therapeutic potential of nucleoside/nucleotide analogues against poxvirus infections. Reviews in medical virology. 2004; 14(5):289-300.
85. Duraffour S, Mertens B, Meyer H, van den Oord JJ, Mitera T, Matthys P, Snoeck R, Andrei G. Emergence of cowpox: study of the virulence of clinical strains and evaluation of antivirals. PLoS One. 2013;8(2):e55808.
86. Yang G, Pevear DC, Davies MH, et al. An orally bioavailable antipoxvirus compound (ST-247) inhibits extracellular virus formation and protects mice from lethal orthopoxvirus challenge. J Virol 2005; 79:13139–13149.
87. Altmann SE, Smith AL, Dyall J, Johnson RF, Dodd LE, Jahrling PB, Paragas J, Blaney JE. Inhibition of cowpox virus and monkeypox virus infection by mitoxantrone. Antiviral Research. 2012;93(2):305-8.
88. Shchelkunov SN, Safronov PF, Totmenin AV, Petrov NA, Ryazankina OI, Gutorov VV, Kotwal GJ. The genomic sequence analysis of the left and right species-specific terminal region of a cowpox virus strain reveals unique sequences and a cluster of intact ORFs for immunomodulatory and host range proteins. Virology. 1998;243(2):432-60.
89. Zipfel PF, Skerka C. Complement regulators and inhibitory proteins. Nature Reviews Immunology. 2009;9(10):729-40.
90. Dunkelberger JR, Song WC. Complement and its role in innate and adaptive immune responses, Cell Research.2010; 20: 34e50.
91. Saifuddin M, Parker CJ, Peeples ME, Gorny MK, Zolla-Pazner S, Ghassemi M, Rooney IA, Atkinson JP, Spear GT. Role of virion-associated glycosylphosphatidylinositol-linked proteins CD55 and CD59 in complement resistance of cell line-derived and primary isolates of HIV-1. The Journal of Experimental Medicine. 1995;182(2):501-9.
92. Spear GT, Lurain NS, Parker CJ, Ghassemi M, Payne GH, Saifuddin M. Host cell-derived complement control proteins CD55 and CD59 are incorporated into the virions of two unrelated enveloped viruses. Human T cell leukemia/lymphoma virus type I (HTLV-I) and human cytomegalovirus (HCMV). Journal of immunology (Baltimore, Md.: 1950). 1995; 155(9):4376-81.
93. Shaw ML, Stone KL, Colangelo CM, Gulcicek EE, Palese P. Cellular proteins in influenza virus particles. PLoS Pathogens. 2008;4(6):e1000085.
94. Mohamed MR, McFadden G. NFκB inhibitors: Strategies from poxviruses. Cell Cycle. 2009;8(19):3125-32.
95. Pickup DJ, Ink BS, Hu WE, Ray CA, Joklik WK. Hemorrhage in lesions caused by cowpox virus is induced by a viral protein that is related to plasma protein inhibitors of serine proteases. Proceedings of the National Academy of Sciences. 1986;83(20):7698-702.