Review

Zoonotic poxviruses☆

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ABSTRACT

Poxviruses compromise a group of long known important pathogens including some zoonotic members affecting lifestock animals and humans. While whole genome sequence analysis started to shed light into the molecular mechanisms underlying host cell infection, viral replication as well as virulence, our understanding of poxvirus maintenance in nature and their transmission to humans is still poor. During the last two decades, reports on emerging human monkeypox outbreaks in Africa and North America, the increasing number of cowpox virus infections in cats, exotic animals and humans and cases of vaccinia virus infections in humans in South America and India reminded us that – beside the eradicated smallpox virus – there are other poxviruses that can cause harm to men. We start to learn that the host range of some poxviruses is way broader than initially thought and that mainly rodents seem to function as virus reservoir. The following review is aiming to provide an up-to-date overview on the epidemiology of zoonotic poxviruses, emphasizing orthopoxviruses. By outlining the current knowledge of poxvirus transmission, we hope to raise the awareness about modes of acquisition of infections and their proper diagnosis.

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Contents

1. Introduction

Poxviruses are among the best and longest known viruses to mankind, and they are among the most feared viruses of lifestock animals and humans. Viruses of the family *Poxviridae* have large and complex virions with a size of approximately 140–260 nm × 220–450 nm that is large enough to be visible by light microscopy. The genome is a double-stranded DNA molecule of 130–375 kbp, with the genome size varying between genera and from strain to strain. Genetic studies showed that the central part (approximately 100 kbp) of the genome is highly conserved in gene order, content and sequences whereas the terminal regions vary both in length and patterns of restriction enzyme cleavage sites (Esposito and Knight, 1985). The availability of full genome sequence data from some poxviruses (www.poxvirus.org) has enabled detailed bioinformatic analyses including the generation of phylogenetic trees. Only members of the subfamily *Chordopoxvirinae* are capable of infecting vertebrate hosts with four genera containing species that induce disease in humans. Three of them also harbor zoonotic potential, namely the genera Orthopoxvirus, Parapoxvirus and Yatapoxvirus (see Table 1) and are focus of this chapter.

2. Orthopoxviruses

The most prominent species of the genus orthopoxvirus (OPV) is variola virus, the causative agent of smallpox. However, since variola virus has no zoonotic potential it will not be addressed in this chapter and the reader is referred to reviews published recently (Parrino and Graham, 2006; Mercer et al., 2007). The genus orthopox-

virus contains three virus species that are important zoonotic pathogens: monkeypox, cowpox and vaccinia virus (Table 1). Orthopoxviruses are immunologically cross-reactive and cross-protective, so that after infection with any member of this genus a protection against an infection with any other member of the genus is obtained. This became for the first time illustrious with the experiments of Edward Jenner in 1798/1799. Vaccinia virus was afterwards "the" vaccine to eradicate smallpox, which was a great success for the World Health Organization in 1980. VACV originates from the Latin word "vacca" for cow, but it is uncertain if VACV really derives from cattle. Cowpox virus ("true cowpox") and pseudocowpox virus ("spurious cowpox", Parapoxvirus) were already described and distinguished by Jenner, too (see Table 1). Monkeypox virus was first described as causes of pox-like illnesses in monkeys in the late sixties of the last century. Since that time the knowledge on poxviruses was increasing with an incredible speed. Another boost became the field of poxvirus research after 9/11 when the world suddenly feared the use of smallpox virus as bio-terroristic agent and efforts were consequently focussing on the development of safe vaccines and effective antiviral drugs. However, because smallpox virus is purely anthropogenic with no know animal reservoir, we here will focus on the three zoonotic OPV listed above.

3. Monkeypox virus

3.1. Monkey monkeypox

Monkeypox was described for the first time as a rash causing illness in captive monkeys in the zoo of

Table 1
Genera of the family *Poxviridae*, subfamily *Chordopoxvirinae*, which contain virus species that are pathogenic to humans.

Genus and virus species	Geographical distribution	Host	Reservoir
Orthopoxvirus			
Variola virus	Eradicated	Human	None
Monkeypox virus	Africa, (USA)[a]	Human, primates (see Table 2)	Squirrels, dormice, gambian giant rat, hedge hog, Jerboa, opossum, woodchuck (see Table 2)
Cowpox virus	Western Eurasia	Human, cat, cow, elephant and zoo animals (see Table 3)	Rodents (see Table 3)
Vaccinia virus[b] (∼buffalopox)	Worldwide	Humans, cattle, buffalos, rabbit	Most likely rodents
Parapoxvirus			
Orf virus (contagious ectyma, contagious pustular dermatitis)	Worldwide	Humans, sheep, goat, artiodactyla, ruminant	Unknown?
Bovine papular stomatitis virus	Worldwide	Humans, cattle	Unknown?
Pseudocowpox virus (paravaccinia, melkers nodule)	Worldwide	Humans, cattle	Unknown?
Parapoxvirus of seals	Worldwide	Humans, seals	Unknown?
Parapoxvirus of reindeer	Finland	Humans, reindeer	Unknown?
Molluscipoxvirus			
Molluscum contagiosum virus	Worldwide	Humans	No
Yatapoxvirus			
Tanapox virus	Africa	Humans	Mosquitoes?, rodents?
Yaba-like disease virus	Africa	Primates	Unknown?
Yaba monkey tumor virus	Africa	Primates	Unknown?

[a] Import of MPXV to the USA with gambian giant rats.
[b] Buffalopox virus is a name historically used for VACV infections in buffalos and sometimes defined as a sub-species of VACV. Because buffalopox virus is officially not a taxonomically assigned name, we here use the phrase buffalopox for the clinical presentation of a VACV infection in buffalos.

Copenhagen in 1957. In the following years several outbreaks have been reported in European and American zoos. In monkeys the disease is characterized by generalized skin eruptions, developing to papules on the trunk, face, palms and soles. Papules subsequently develop into vesicles and scabs which usually fall off after about 10 days after the rash developed. The severity of the disease varies with regard to the host species, e.g. it is mild in Cynomolgus monkeys (*Macaca cynomolgus*), but more severe in orang utans (*Pongo* sp.) (Arita et al., 1972; Zaucha et al., 2001). Based on its distinct phenotype monkeypox virus (MPXV) is regarded as a discrete species within the genus orthopoxvirus. Epidemiological investigations demonstrated that the virus is endemic in squirrels in the tropical rainforest of Africa (see Table 2).

3.2. Human monkeypox

Human monkeypox was reported for the first time in the 1970s in countries of Western and Central Africa (Jezek et al., 1986). This was at the time when variola virus, the causative agent of smallpox, was already eradicated in those regions. WHO initiatives resulted in an intensive investigation campaign of rash causing illnesses from 1970 to 1986. These investigations showed that the etiological agent was indeed MPXV with a case fatality rate of up to 10–17%. The secondary attack rate (3%) was much lower than that of smallpox (up to 80% in non-immunized contacts). After the WHO campaign only few cases of monkeypox have been reported until 1996. In 1996/1997 and 2001–2004 large human monkeypox outbreaks were reported in the Democratic Republic of Congo (DRC) (Rimoin et al., 2007). In 1996/1997 the mortality was low (1.5%), but the secondary attack rate was high (up to 78%). This was explained by a reduced immunity due to the abolished mandatory smallpox vaccination. The very unspecific case definition in the 1996/1997 outbreak and intensified lab investigations (Rimoin et al., 2007) also led to the conclusion that clinically similar chickenpox caused by Varicella zoster virus (a herpesvirus) may have been responsible for many cases. Chickenpox is characterized by a high secondary transmission rate up to 85% (Di Giulio and Eckburg, 2004). Laboratory analysis of suspected human 136 monkeypox cases from the DRC between 2001 and 2004 demonstrated 45% chickenpox infection and 38% MPXV infection. This supports that many cases of the 1996/1997 outbreak were indeed chickenpox (Rimoin et al., 2007).

In 2005 emergence of occasional human monkeypox virus infections were for the first time reported from

Table 2
Different hosts of monkeypox virus as demonstrated by serological evidence, PCR (*) and/or virus isolation.

Order/family	Species	Virus isolated	Proven transmission to men
Primates/*Hominidae*	Chimpanzee (*Pan troglodytes*)	No	No
	Orangutan (*Pongo* sp.)	Yes	Yes
Primates/*Cercopithecidae*	Cynomolgus monkey (*Macaca cynomolgus*)	Yes	Yes
	Mona monkey (*Cercopithecus mona*)	No	No
	Black-cheeked white-nosed/red-tailed monkey (*Cercopithecus ascanius*)	No	No
	Greater spot-nosed monkey (*Cercopithecus nictitans*)	No	No
	Lesser spot-nosed monkey (*Cercopithecus petaurista*)	No	No
	Grivet (*Cercopithecus aethiops*)	No	No
	Allen's swamp monkey (*Allenopithecus nigroviridis*)	No	No
	Tana river/agile/crested mangabey (*Cercocebus galeritus*)	No	No
Primates/*Colobinae*	Western red colobus (*Piliocolobus badius*)	No	No
Artiodactyla/*Suidae*	Domestic pig (*Sus scrofa*)	No	No
Erinaceomorpha/*Erinaceidae*	African hedge hog (*Atelerix* spp.)	No*	No
Didelphimorphia/*Didelphidae*	Gray short-tailed opossum (*Monodelphis domestica*)	No*	No
	Southern/common opossum (*Didelphis marsupialis*)	No*	No
Rodentia/*Sciuridae*	Rope squirrel (*Funisciurus* sp.)	Yes	Yes
	Ribboned rope squirrel (*Funisciurus lemniscatus*)	No	No
	Thomas's rope squirrel (*Funisciurus anerythrus*)	Yes	No
	Lady Burton's rope squirrel (*Funisciurus ilsabella*)	No	No
	Congo rope squirrel (*Funisciurus congicus*)	No	No
	Gambian sun squirrel (*Heliosciurus gambianus*)	No	No
	Red-legged sun squirrel (*Heliosciurus rufobrachium*)	No	No
	Prairie dogs (*Cynomys* sp.)	Yes	Yes
	Black-tailed prairie dog (*Cynomys ludovicianus*)	No*	No
	Woodchuck (*Marmota monax*)	No*	No
Rodentia/*Gliridae*	Dormouse (*Graphiurus* spp.)	Yes	
Rodentia/*Hystricidae*	African brush-tailed porcupine (*Atherurus africanus*)	No	No
Rodentia/*Nesomyidae*	Gambian giant rat (*Cricetomys* sp.)	Yes	No
	Emin's pouched rat/Gambian rat (*Cricetomys emini*)	No	No
Rodentia/*Dipodidae*	Jerboa (*Jaculus* spp.)	No*	No
Macroscelidea/*Macroscelididae*	Four-toed elephant shrew/Sengi (*Petrodromus tetradactylus*)	No	No

Southern Sudan, a rural farming area which ecologically differs tremendously from the tropical rainforest. A follow-up investigation by the WHO found evidence of sporadic cases of monkeypox in this area, supporting the thesis of recurrent carry-over from local, supposed animal reservoirs (Damon et al., 2006).

3.3. Monkeypox in the USA

Monkeypox is an "emerging disease" not only in Africa because in 2003 it was accidentally introduced into the USA. In summary, 71 human cases were reported, 26% of the patients had to be hospitalized. The particular MPXV strain responsible here seems to have originated from MPXV-infected rodents imported from Ghana. The rodents had been transported and kept with native prairie dogs that were afterwards distributed as pets (Croft et al., 2007). Human cases mostly occurred in staff of veterinary facilities seeing ill prairie dogs, in households with prairie dogs, in pet store visitors and employees (59% of the cases occurred among occupationally exposed persons). A recent risk factor analysis revealed that bites and exposure to excretions, secretions and respiratory droplets of MPXV-infected animals can result in infection (Reynolds et al., 2007). However, the MPXV from the USA had a very low virulence with no fatalities (Chen et al., 2005). Comparison of different MPXV strains showed that there exist two distinct clades, namely a Western Africa/US and a Central Africa clade. Clinical and pathological characteristics of experimental infection of prairie dogs and ground squirrels with representative MPXV strains demonstrated that the Western Africa/US strains are less virulent than the Central Africa strains (Tesh et al., 2004; Xiao et al., 2005; Sbrana et al., 2007). This explains the lack of severe human cases during the 2003 US outbreak. A recent in vivo study with infection trials in prairie dogs demonstrated that a viral complement control protein (C3L) missing in the Western Africa/US strains but present in the Central Africa strains might be one of the potential factors influencing the severity of the pathogenicity. The emergence of MPXV in the USA resulted in comprehensive studies of imported animals in the USA and also animal reservoirs in Africa (for details of investigated animals see Table 2, Hutson et al., 2007; Parker et al., 2007). A model for the ecological niche of MPXV in Africa was published recently (Levine et al., 2007): it predicts that the occurrence of MPXV coincides with the distribution of humid lowland evergreen tropical forest across Africa.

Today, monkeypox is regarded as the most important poxvirus infection of humans after the eradication of smallpox. In particular for immune-comprised individuals infections could be risky. Thus a change in the natural transmission patterns of MPXV infections in Africa may strongly be influenced by the increase of an HIV-infected population and vice versa. The 2003 US outbreak also demonstrated that the disease is not confined to certain parts of Africa, but may show up in other areas of the world as well. Hence, monkeypox virus is another example demonstrating how vulnerable we all are to so-called exotic pathogens.

4. Vaccinia virus

For decades vaccinia virus (VACV) was used for the immunization of humans during the smallpox eradication campaign. Besides the paramount achievement of VACV as vaccine, several serious complications have been reported, with the frequency depending on the vaccine strain (Mercer et al., 2007; CDC, 2008). Serious complications included, e.g. progressive vaccinia, generalized vaccinia, vaccinia eczematum, sometimes neurological disorders (encephalitis), myocarditis or ocular complications. Numerous strains exist which differ in their biological properties and virulence in man and in animal models (for review see Mercer et al., 2007). Today, VACV is used in many laboratories worldwide as a vector for the generation of recombinant vaccine candidates capable of safely expressing foreign proteins such as the rabies virus glycoprotein (Cliquet et al., 2008) or the gag and/or env genes of Visna/Maedi virus (Reina et al., 2008) or for a new tuberculosis vaccine (Hawkridge et al., 2008). Lab infections with VACV, e.g. by needlesticks or scratches of laboratory workers have been reported (CDC, 2008).

However, due to fears that smallpox might be used in bioterrorism, VACV remains also in the focus of the public as poxvirus vaccine. Many countries have acquired stocks of first and second generation of VACV vaccines. Today, the highly attenuated VACV strain modified vaccinia virus Ankara (MVA) which was developed in the 1970s by more than 500 passages (Mayr et al., 1978) is regarded as a promising so-called third generation smallpox vaccine candidate due to the lack of side effects in comparison to the existing vaccines (Drexler et al., 2004; Gómez et al., 2008).

Vaccine escape has been hypothesized to account for some VACV strains isolated from domestic animals, including rabbitpox 1932 in New York and 1941 in Utrecht/The Netherlands, horsepox 1976 in Mongolia, and endemic buffalopox in India. However, after sequencing of full genomes of horsepox and Utrecht rabbitpox virus (Li et al., 2005), the vaccine escape hypothesis has been disproved. For both these strains the presence of additional cowpox virus (CPXV)-like sequences abolished speculations on their origin as a VACV escape (Tulman et al., 2006). Phylogenetic analysis based on three genes also confirmed that buffalopox virus (BPXV) is closely related to VACV, taxonomically it is like the other two agents a strain of VACV (Singh et al., 2006; for details of taxonomy see http://www.ncbi.nlm.nih.gov/ICTVdb/Ictv/fs_poxvi.htm).

4.1. Buffalopox virus

BPXV was for the first time isolated in 1967 in Northern India and still is associated with sporadic outbreaks in Asian buffalos (Bubalus bubalis) in Pakistan, India, Bangladesh, Russia, Indonesia, Egypt, and Italy. The disease is characterized by severe local pocks affecting the udder and teats, leading to mastitis thereby undermining the productivity of milk animals (40–70% reduction) and thus having an impact on the respective dairy industry. In 2003 an outbreak occurred in 10 herds with an overall morbidity

of 45% in Maharashtra State, India. Some animals also exhibit lesions on the hindquarters, suggesting secondary or even a generalized infection. Milkers accidently get pox-like local lesions on their hands, forearms and forehead accompanied with fever, axillary lymphadenopathy and general malaise (Singh et al., 2007). In the following years 2004–2005 a nosocomial outbreak of BPXV in humans has been reported from the five major burn units of the city Karachi in Pakistan. Here, patients developed pox lesions at burn wounds and the intact skin surrounding them. The source of infection had been VACV contaminated buffalo fat that was used as first-aid supplies for covering the burns. Despite the tragedy and irony of these infections, it proved an efficient indirect transmission mode of an OPV (Zafar et al., 2007).

4.2. Brazilian vaccinia viruses

Starting in 1999 several VACV strains were shown to be responsible for zoonotic disease affecting more than 1100 dairy cattle and up to 80% of their handlers in rural tropical rainforest and woodland savanna areas in southeast Brazil (Trindade et al., 2006, 2007a,b). Cows had lesions on their teats characterized by papules that evolved to ulcers. Comparable to BPXV infections, milkers presented pleio-morphic lesions on their hands (mainly papules and painful ulcers), fever, and lymphadenopathy. Several vaccinia virus-like viruses have been isolated and named according to their geographic origin, i.e. isolates Aracatuba, Cantalago, Guarani, Passatempo. In addition, a virus has been isolated from sentinel mice (isolate Belo Horizonte). In Brazil the emerging disease seems to be endemic. Initial hypotheses on the reasons for the occurrence of VACV in these areas of South America involved a long-term survival of VACV vaccine strains in nature. Orthopoxviruses are known to have a high tenacity (Essbauer et al., 2007), which indeed could account for such a phenomenon. However, recent phylogenetic studies provided evidence that it is unlikely that Brazilian isolates have derived from a single vaccine strain used during the past century (Trindade et al., 2007a,b).

4.3. Cowpox virus—an emerging virus with a broad host range

Until 40 years ago CPXV was seen in milking cows with occasional zoonotic transmission on the hands of milkers by contact to pocks on the teats. Sometimes auto-inoculation led to secondary pocks on other parts of the body (Baxby and Bennett, 1997). Today, CPXV is known to naturally infect a very broad range of host species in Western Eurasia (Table 3), such as cats, various zoo animals and humans. For domestic cats more than 400 cases of CPXV infections have been described (Bennett et al., 1986, 1989; Mahnel, 1991; Hinrichs et al., 1999; Brown et al., 1989; Baxby et al., 1994; Pfeffer et al., 2002; Müller et al., 2004), but it is supposed that many infections are not recognized by veterinarians and/or owners. In domestic and also large cats multiple skin lesions (primarily seen on head, oral cavity, neck, forelimb or paws), conjunctivitis or purulent ocular discharge develop upon infection. Occasionally systemic infections occur that may end fatal if inner organs as the lungs (e.g. necrotizing pneumonia), co-infections or immune-deficiency are involved (Bennett et al., 1986, 1989). Cat-to-cat transmission is apparently rare (Bennett et al., 1986). The outcome of the infection seems to depend on the CPXV strain, route and site of administration and most likely the dose of infection. The real incidence of CPXV in cats may be reflected by serological data; here a variation from 0 up to 16% cats with antibodies against CPXV (OPV, respectively) are reported from England, Norway, Austria, Germany and Finland (Juncker-Voss et al., 2004). There is a seasonal variation with an accumulation of CPXV infections in late summer and autumn (Bennett et al., 1986; Pfeffer et al., 2002). Cats as predators are exposed to CPXV while hunting rodents which serve as a reservoir for CPXV (Pfeffer et al., 2002). Beside cats, many CPXV infections have been reported from zoo and circus elephants. The latter can suffer severe CPXV infections and valuable animals have to be put on human ground. Whether or not this is a consequence of unequate holding conditions and/or the individual physical situation remains unknown (Wisser et al., 2001). Hence, vaccination of these animals is very crucial and vaccinia virus MVA strain (see above) is admissible for vaccination of zoo animals in the EU. Vaccination was shown to protect rabbits against a dermal and intradermal challenge infection with a German CPXV (Munz et al., 1993) and seems to protect elephant and rhinozeros kept in zoos and circuses (own unpublished results).

4.4. Human cowpox

Human CPXV cases are mainly caused by direct contact to "cuddly" cats (Baxby et al., 1994), in rare cases, e.g. by rats or zoo animals (Table 3). The infection can spread to other close contacts, and transmission involving up to three individuals has been described (Coras et al., 2005). Infections are characterized by localized pustular skin lesions, mostly on the hands. Scratches or abrasions of the skin may determine localization of the lesions elsewhere, e.g. on face, neck or feet. Systemic involvement and/or fatal outcome of human CPXV infections have been reported only for immune-comprised individuals thus far (Czerny et al., 1991; Pelkonen et al., 2003). Infections of humans may become more numerous due to the lack of an absent or adequate immune status of the population because of the abrogated, but cross-protective smallpox vaccination in the 1980s.

4.5. Reservoir of cowpox virus

Like all above-mentioned animal host species (cows, cats, elephants, etc.) humans are default hosts of CPXV, while several wild rodent species act as a reservoir for CPXV (Table 3). Serological and PCR data from Great Britain, Norway, Sweden, Finland, Russia and Germany confirmed that different vole species, mice and gerbils (see Table 3) serve as a natural reservoir for CPXV. In recent years transmission by (sometimes also cuddly) rats to other host species including humans "emerged" (e.g. Wolfs

Table 3
Different hosts of cowpox virus as demonstrated by serological evidence and/or virus isolation.

Order/family	Species	Virus isolated	Proven transmission to men
Primates/*Cercopithecidae*	Barbary macaque (*Macaca sylvanus*)	No	No
Primates/*Callitrichidae*	Marmorset (*Callithrix jaccus*)	Yes	No
Carnivora/*Felidae*	Cat (*Felis sylvestris f. Catus*)	Yes	Yes
	Cheetah (*Acinonyx jubatus*)	Yes	Yes
	Lynx (*Lynx lynx*)	No	No
	Lion (*Panthera leo*)	Yes	No
	Black panther (*Panthera padus*)	Yes	No
	Ocelot (*Felis pardalis*)	Yes	No
	Jaguar (*Felis onca*)	Yes	No
	Puma (*Felis concolor*)	Yes	No
	Far eastern cat (*Felis bengalis*)	No	No
	Jaguarundi (*Herpailurus yaguarondi*)	Yes	No
Carnivora/*Herpestidae*	Banded mongoose (*Mungos mungo*)	Yes	No
Carnivora/*Canidae*	Dog (*Canis lupus familiaris*)	Yes	No
	Fox (*Vulpes vulpes*)	No	No
	Arctic fox (*Alopex lagopus*)	No	No
Carnivora/*Mustelidae*	Stone marten (*Martes martes*)	No	No
Carnivora/*Ailuridae*	Bearcat (*Aiulurus fulgens*)	Yes	No
Artiodactyla/*Suidae*	Wild boar (*Sus scrofa*)	No	No
Artiodactyla/*Giraffidae*	Okapi (*Okapia johnstoni*)	Yes	No
Artiodactyla/*Bovidae*	Cow (*Bos taurus*)	Yes	Yes
Artiodactyla/*Camelidae*	Lama (*Lama glama pacos*)	No	No
Perissodactyla/*Equidae*	Horse (*Equus caballus*)	Yes	No
Perissodactyla/*Rhinocerotidae*	Black rhinoceros (*Diceros bicornis*)	Yes	No
	White rhinoceros (*Ceratotherium s. simum*)	Yes	No
Perissodactyla/*Tapiridae*	Tapir (*Tapirus indicus*)	Yes	No
Proboscidea/*Elephantidae*	Asian elephant (*Elephas maximus*)	Yes	Yes
	African elephant (*Loxodonta africana*)	Yes	No
Pilosa/*Myrmecophagidae*	Anteaters (*Myrmecophaga tridactyla*)	No	No
Rodentia/*Castoridae*	Beaver (*Castor fibor canadensis*)	Yes	No
Rodentia/*Arvicolidae*	Bank voles (*Myodes glareolus*)	No	No
	Gray-sided vole (*Clethrionomys. rufocanus*)	No	No
	Red-backed voles (*C. rutilus*)	No	No
	Field vole (*Microtus agrestis*)	Yes	No
	Root vole (*Microtus oeconomus*)	No	No
Rodentia/*Muridae*	Wood mice (*Apodemus sylvaticus*)	No	No
	Yellow-necked mice(*Apodemus flavicollis*)	No	No
	House mice (*Mus musculus*)	No	No
	Common rat (*Rattus norvegicus*)	Yes	Yes
	Giant gerbil (*Rhombomys opimus*)	Yes	No
	Gerbil (*Meriones lybicus*)	Yes	No
Rodentia/*Sciuridae*	Ground squirrel (*Citellus fulvus*)	No	No
Rodentia/*Caviidae*	Patagonian cavy (*Dolichotis patagonum*)	No	No
Insectivora/*Soricidae*	Common shrew (*Sorex araneus*)	No	No

et al., 2002; Martina et al., 2006; Kurth et al., 2008; Ninove et al., 2009; Campe et al., 2009). Consequently, these reports lead to the assumption that this particular reservoir may have been underestimated but that many rodent species may serve as a reservoir for CPXV.

The CPXV isolates investigated so far display a high and more complex heterogeneity in comparison to other OPV species. Comparison of restriction enzyme fragment profiles and partial sequencing of some genes showed that several CPXV strains seem to regionally and timely co-circulate in Germany (Meyer et al., 1999; Meyer, unpublished data) while in England one CPXV strain seems to dominate. Genetic analysis of full genomes is sparse with only two old CPXV existing. However, in depths analyses of more CPXV strains are currently under investigation. The results may shed light into the origin of the various CPXV strains. Future will tell if CPXV disease might increase in importance, whether as a result of a change either in the epidemiology of the disease, in the reservoir host, or in the nature of the dominant biotype of the virus itself.

4.6. Parapoxviruses and yatapoxviruses

Parapoxviruses form a divergent group of viruses with zoonotic parapoxvirus (PPV) infections mainly reported from persons with close contact to sheep and cattle. Infections are usually benign and only local lesions develop mostly on the hands. The majority of human cases are

caused by Orf virus (ORFV). In flocks the incidence can be as high as 90%, but the mortality is usually low. Pseudocowpox virus (PCPV, syn. Milker's nodule virus, paravaccinia virus), bovine popular stomatitis virus (BPSV, syn. bovine popular stomatitis virus) and parapoxvirus of red deer in New Zealand (PVNZ) are also listed as PPV species. In the last decade infections of different seal species (e.g. *Callorhinus ursinus*, *Phoca virulina*, *Halichoerus grypus*, *Leptonychotes weddellii*), sea lions (e.g. *Zaophus californianus*, *Otaria bryonia*), camels (*Camelus dromedaries*), Japanese serow (*Capricornis crispus*), and further deer species (e.g. *Cervus nippon centralis*, *Rangifer tarandus tarandus*) with parapoxviruses were described with a yet unclear zoonotic potential (Büttner and Rziha, 2002; Mercer et al., 2007; see Table 1).

In comparison to the worldwide occurrence of parapoxvirus infections, yatapoxvirus infection is a rare exotic, mild disease mostly characterized by vesicular skin lesions in humans (Tanapox virus) or monkeys (Yaba-like disease virus), or focalized epidermal histiocytomas (Yaba monkey tumor virus). Natural infections are reported from equatorial Africa, i.e. Kenia, Kongo. So far, only around a dozen case reports from monkeys and humans have been published (e.g. Stich et al., 2002; Dhar et al., 2004). The disease may play a minor role in primates kept in zoos, e.g. African green monkey (*Cercopithecus aethiops*), baboons (*Papio cynocephalus anubis*, *Papio papio*), rhesus monkeys (*Mucaca mulatta*), bonnet (*Mucaca radiata*) and Asiatic cynomolgus (*Macaca iris*). Although the speed of disease progression of the various para- and yatapoxviruses varies considerably, the direct contact to a pox lesion or an immediate contact to contaminated items with skin is thought to be required for an infection. For more indepth reviews on zoonotic aspects of parapoxviruses and yatapoxviruses the respective chapters of the recently published book "Poxviruses" by Mercer et al., 2007 are recommended.

5. Diagnosis

The classical and first-line tool for the diagnosis of poxviruses in swabs or bioptates is electron microscopy: virus particles with their typical morphology are usually present in sufficient amounts. Today, PCR, real-time PCR and sequencing are the methods of choice for a rapid identification and differentiation of poxviruses up to the species level (for details see Mercer et al., 2007). OPVs can be easily isolated in various cell cultures for further characterization. In histological sections an infection can be proven for some agents (e.g. TANV, CPXV) by epithelial hyperplasia. A pathognomic feature for CPXV is the presence of large eosinophilic A-type inclusion bodies (ATI) in the cytoplasm. Retrospective infections are diagnosed by serological assays such as the neutralization test.

However, suspicious cases of either vaccinia, monkeypox or cowpox virus infections cannot be diagnosed based on their clinical presentations alone. It has to be emphasized that the laboratory in charge should have expertise in the panel of techniques mentioned that is required for confirmative diagnosis.

Differential diagnoses of poxviral infections in humans include the following: MPXV infections can be mistaken by chickenpox infections as clinical symptoms are almost identical. At the onset of diseases caused by most poxvirus infections when erythema, edema, papules or nodules with blisters appear, e.g. Herpes simplex virus-1 and -2, beta-hemolysing *Streptococcus* of group A, *Staphylococcus aureus*, *Haemophilus influenzae*, *Neisseria pneumonia*, *Bartonella henselae* should be concerned. In the later course of the disease, i.e. if ulcers and crusts are present, agents such as *Bacillus anthracis*, *Francisella tularensis* or *Treponema pallidum* also should be taken into account. Bacterial and fungal secondary infections have been reported for human and animal hosts.

Occupational risk for poxvirus infections has been reported, e.g. for cow workers (PPV), health care workers (VACV), animal traders (MPXV) and animal keepers (MPXV, CPXV) (Reynolds et al., 2007; Croft et al., 2007; Juncker-Voss et al., 2004; Trindade et al., 2007a; Kurth et al., 2008). For monkeypox the CDC has published interim guidelines for veterinarians and animal traders (http://www.cdc.gov/ncidod/monkeypox/pet.htm).

Conflict of interest statement

None.

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