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Zoonotic poxviruses

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15 The findings and conclusions in this report are those of the authors and do not
16 necessarily represent the views of the Bundeswehr Institute of Microbiology.

17

18 **Key words**

19 Pox, orthopox, monkeypox, cowpox, parapox, transmission, reservoir hosts

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21

22 **Abstract**

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

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49 Introduction

50 Poxviruses are among the best and longest known viruses to mankind, and they are
51 among the most feared viruses of livestock animals and humans. Viruses of the family
52 Poxviridae have large and complex virions with a size of approximately 140-260 nm x
53 220-450 nm that is large enough to be visible by light microscopy. The genome is a
54 double-stranded DNA molecule of 130-375 kbp, with the genome size varying
55 between genera and from strain to strain. Genetic studies showed that the central
56 part (approximately 100 kbp) of the genome is highly conserved in gene order,
57 content and sequences whereas the terminal regions vary both in length and patterns
58 of restriction enzyme cleavage sites (Esposito & Knight, 1985). The availability of full
59 genome sequence data from some poxviruses (www.poxvirus.org) has enabled
60 detailed bioinformatic analyses including the generation of phylogenetic trees. Only
61 members of the subfamily *Chordopoxvirinae* are capable of infecting vertebrate hosts
62 with four genera containing species that induce disease in humans. Three of them
63 also harbor zoonotic potential, namely the genera Orthopoxvirus, Parapoxvirus and
64 Yatapoxvirus (see table 1) and are focus of this chapter.

65

66 Orthopoxviruses

67 The most prominent species of the genus *orthopoxvirus* (OPV) is variola virus, the
68 causative agent of smallpox. However, since variola virus has no zoonotic potential it
69 will not be addressed in this chapter and the reader is referred to reviews published
70 recently (Parrino & Graham, 2006; Mercer et al., 2007). The genus *orthopoxvirus*
71 contains three virus species that are important zoonotic pathogens: monkeypox,
72 cowpox and vaccinia virus (table 1). Orthopoxviruses are immunologically cross-
73 reactive and cross-protective, so that after infection with any member of this genus a
74 protection against an infection with any other member of the genus is obtained. This
75 became for the first time illustrious with the experiments of Edward Jenner in 1798/9.
76 Vaccinia virus was afterwards “the” vaccine to eradicate smallpox, which was a great
77 success for the World Health Organization in 1980. VACV originates from the Latin
78 word “vacca” for cow, but it is uncertain if VACV really derives from cattle. Cowpox
79 virus (“true cowpox”) and pseudo cowpox virus (“spurious cowpox”, Parapoxvirus)
80 were already described and distinguished by Jenner, too (see table 1). Monkeypox

81 virus was first described as causes of pox-like illnesses in monkeys in the late sixties
82 of the last century. Since that time the knowledge on poxviruses was increasing with
83 an incredible speed. Another boost became the field of poxvirus research after 9/11
84 when the world suddenly feared the use of smallpox virus as bio-terroristic agent and
85 efforts were consequently focussing on the development of safe vaccines and
86 effective antiviral drugs. However, because smallpox virus is purely anthropogenic
87 with no know animal reservoir, we here will focus on the three zoonotic OPV listed
88 above.

89

90 **Monkeypox virus**

91 Monkey monkeypox

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

104 Human monkeypox

105 Human monkeypox was reported for the first time in the 1970s in countries of
106 Western and Central Africa (Jezek et al., 1986). This was at the time when variola
107 virus, the causative agent of smallpox, was already eradicated in those regions.
108 WHO initiatives resulted in an intensive investigation campaign of rash causing
109 illnesses from 1970-1986. These investigations showed that the etiological agent was
110 indeed MPXV with a case fatality rate of up to 10-17%. The secondary attack rate
111 (3%) was much lower than that of smallpox (up to 80% in non-immunized contacts).

112 After the WHO campaign only few cases of monkeypox have been reported until
113 1996. In 1996/1997 and 2001-2004 large human monkeypox outbreaks were
114 reported in the Democratic Republic of Congo (DRC) (Rimoin et al., 2007). In
115 1996/1997 the mortality was low (1.5%), but the secondary attack rate was high (up
116 to 78%). This was explained by a reduced immunity due to the abolished mandatory
117 smallpox vaccination. The very unspecific case definition in the 1996/1997 outbreak
118 and intensified lab investigations (Rimoin et al., 2007) also led to the conclusion that
119 clinically similar chickenpox caused by Varicella zoster virus (a herpesvirus) may
120 have been responsible for many cases. Chickenpox is characterized by a high
121 secondary transmission rate up to 85% (Di Giulio & Eckburg, 2004). Laboratory
122 analysis of of suspected human 136 monkeypox cases from the DRC between 2001
123 and 2004 demonstrated 45% chickenpox infection and 38% MPXV infection. This
124 supports that many cases of the 1996/97 outbreak were indeed chickenpox (Rimoin
125 et al., 2007).

126 In 2005 emergence of occasional human monkeypox virus infections were for the first
127 time reported from Southern Sudan, a rural farming area which ecologically differs
128 tremendously from the tropical rainforest. A follow-up investigation by the WHO found
129 evidence of sporadic cases of monkeypox in this area, supporting the thesis of
130 recurrent carry-over from local, supposed animal reservoirs (Damon et al., 2007).

131 Monkeypox in the USA

132 Monkeypox is an “emerging disease” not only in Africa because in 2003 it was
133 accidentally introduced into the USA. In summary, 71 human cases were reported,
134 26% of the patients had to be hospitalized. The particular MPXV strain responsible
135 here seems to have originated from MPXV-infected rodents imported from Ghana.
136 The rodents had been transported and kept with native prairie dogs that were
137 afterwards distributed as pets (Croft et al., 2007). Human cases mostly occurred in
138 staff of veterinary facilities seeing ill prairie dogs, in households with prairie dogs, in
139 pet store visitors and employees (59% of the cases occurred among occupationally
140 exposed persons). A recent risk factor analysis revealed that bites and exposure to
141 excretions, secretions and respiratory droplets of MPXV-infected animals can result
142 in infection (Reynolds et al., 2007). However, the MPXV from the USA had a very low
143 virulence with no fatalities (Chen et al., 2005). Comparison of different MPXV strains
144 showed that there exist two distinct clades, namely a Western Africa/US and a

145 Central Africa clade. Clinical and pathological characteristics of experimental
146 infection of prairie dogs and ground squirrels with representative MPXV strains
147 demonstrated that the Western Africa/US strains are less virulent than the Central
148 Africa strains (Tesh et al., 2004; Xiao et al., 2005; Sbrana et al., 2007). This explains
149 the lack of severe human cases during the 2003 US outbreak. A recent *in vivo* study
150 with infection trials in prairie dogs demonstrated that a the viral complement control
151 protein (C3L) missing in the Western Africa/US strains but present in the Central
152 Africa strains might be one of the potential factors influencing the severity of the
153 pathogenicity. The emergence of MPXV in the USA resulted in comprehensive
154 studies of imported animals in the USA and also animal reservoirs in Africa (for
155 details of investigated animals see table 2, Hutson et al., 2007; Parker et al., 2007). A
156 model for the ecological niche of MPXV in Africa was published recently (Levine et
157 al., 2007): it predicts that the occurrence of MPXV coincides with the distribution of
158 humid lowland evergreen tropical forest across Africa.

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

167

168 **Vaccinia virus**

169 For decades vaccinia virus (VACV) was used for the immunization of humans during
170 the smallpox eradication campaign. Besides the paramount achievement of VACV as
171 vaccine, several serious complications have been reported, with the frequency
172 depending on the vaccine strain (Mercer et al., 2007; CDC, 2008). Serious
173 complications included e.g. progressive vaccinia, generalized vaccinia, vaccinia
174 eczematum, sometimes neurological disorders (encephalitis), myocarditis or ocular
175 complications. Numerous strains exist which differ in their biological properties and
176 virulence in man and in animal models (for review see Mercer et al., 2007). Today,

177 VACV is used in many laboratories world-wide as a vector for the generation of
178 recombinant vaccine candidates capable of safely expressing foreign proteins such
179 as the rabies virus glycoprotein (Cliquet et al., 2008) or the gag and/or env genes of
180 Visna/Maedi virus (Reina et al., 2008) or for a new tuberculosis vaccine (Hawkrige
181 et al., 2008). Lab infections with VACV e.g. by needlesticks or scratches of laboratory
182 workers have been reported (CDC, 2008).

183 However, due to fears that smallpox might be used in bioterrorism, VACV remains
184 also in the focus of the public as poxvirus vaccine. Many countries have acquired
185 stocks of first and second generation of VACV vaccines. Today, the highly attenuated
186 VACV strain modified vaccinia virus Ankara (MVA) which was developed in the
187 1970s by more than 500 passages (Mayr et al., 1978) is regarded as a promising so-
188 called third generation smallpox vaccine candidate due to the lack of side effects in
189 comparison to the existing vaccines (Drexler et al., 2004; Gomez et al., 2008).

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

201 Buffalopox virus

202 BPXV was for the first time isolated in 1967 in Northern India and still is associated
203 with sporadic outbreaks in Asian buffaloes (*Bubalus bubalis*) in Pakistan, India,
204 Bangladesh, Russia, Indonesia, Egypt, and Italy. The disease is characterized by
205 severe local pocks affecting the udder and teats, leading to mastitis thereby
206 undermining the productivity of milk animals (40-70% reduction) and thus having an
207 impact on the respective dairy industry. In 2003 an outbreak occurred in 10 herds
208 with an overall morbidity of 45% in Maharashtra State, India. Some animals also

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

219 Brazilian vaccinia viruses

220 Starting in 1999 several VACV strains were shown to be responsible for zoonotic
221 disease affecting more than 1100 dairy cattle and up to 80% of their handlers in rural
222 tropical rainforest and woodland savanna areas in southeast Brazil (Trindade et al.,
223 2006, 2007). Cows had lesions on their teats characterized by papules that evolved
224 to ulcers. Comparable to BPXV infections, milkers presented pleiomorphic lesions on
225 their hands (mainly papules and painful ulcers), fever, and lymphadenopathy. Several
226 vaccinia virus-like viruses have been isolated and named according to their
227 geographic origin, i.e. isolates Aracatuba, Cantalago, Guarani, Passatempo. In
228 addition, a virus has been isolated from sentinel mice (isolate Belo Horizonte). In
229 Brazil the emerging disease seems to be endemic. Initial hypotheses on the reasons
230 for the occurrence of VACV in these areas of South America involved a long-term
231 survival of VACV vaccine strains in nature. Orthopoxviruses are known to have a
232 high tenacity (Essbauer et al., 2007), which indeed could account for such a
233 phenomenon. However, recent phylogenetic studies provided evidence that it is
234 unlikely that Brazilian isolates have derived from a single vaccine strain used during
235 the past century (Trindade et al., 2007).

236

237 **Cowpox virus – an emerging virus with a broad host range**

238 Until 40 years ago CPXV was seen in milking cows with occasional zoonotic
239 transmission on the hands of milkers by contact to pocks on the teats. Sometimes
240 auto-inoculation led to secondary pocks on other parts of the body (Baxby & Bennett,

241 1997). Today, CPXV is known to naturally infect a very broad range of host species
242 in Western Eurasia (table 3), such as cats, various zoo animals and humans. For
243 domestic cats more than 400 cases of CPXV infections have been described
244 (Bennett et al., 1986, 1989; Mahnel, 1991; Hinrichs et al., 1999; Brown et al., 1989;
245 Baxby et al., 1994; Pfeffer et al., 2002; Müller et al., 2004), but it is supposed that
246 many infections are not recognized by veterinarians and/or owners. In domestic and
247 also large cats multiple skin lesions (primarily seen on head, oral cavity, neck,
248 forelimb or paws), conjunctivitis or purulent ocular discharge develop upon infection.
249 Occasionally systemic infections occur that may end fatal if inner organs as the lungs
250 (e.g. necrotizing pneumonia), co-infections or immune-deficiency are involved
251 (Bennett et al., 1986, 1989). Cat-to-cat transmission is apparently rare (Bennett et al.,
252 1986). The outcome of the infection seems to depend on the CPXV strain, route and
253 site of administration and most likely the dose of infection. The real incidence of
254 CPXV in cats may be reflected by serological data; here a variation from 0 to up to
255 16% cats with antibodies against CPXV (OPV, respectively) are reported from
256 England, Norway, Austria, Germany and Finland (Juncker-Voss et al., 2004). There
257 is a seasonal variation with an accumulation of CPXV infections in late summer and
258 autumn (Bennett et al., 1986; Pfeffer et al., 2002). Cats as predators are exposed to
259 CPXV while hunting rodents which serve as a reservoir for CPXV (Pfeffer et al.,
260 2002). Beside cats, many CPXV infections have been reported from zoo and circus
261 elephants. The latter can suffer severe CPXV infections and valuable animals have to
262 be put on human ground. Whether or not this is a consequence of unequated holding
263 conditions and/or the individual physical situation remains unknown (Wisser et al.,
264 2001). Hence, vaccination of these animals is very crucial and vaccinia virus MVA
265 strain (see above) is admissible for vaccination of zoo animals in the EU. Vaccination
266 was shown to protect rabbits against a dermal and intradermal challenge infection
267 with a German CPXV (Munz et al., 1993) and seems to protect elephant and
268 rhinoceros kept in zoos and circuses (own unpublished results).

269 Human cowpox

270 Human CPXV cases are mainly caused by direct contact to “cuddly” cats (Baxby et
271 al., 1994), in rare cases e.g. by rats or zoo animals (table 3). The infection can
272 spread to other close contacts, and transmission involving up to three individuals has
273 been described (Coras et al., 2005). Infections are characterized by localized

274 pustular skin lesions, mostly on the hands. Scratches or abrasions of the skin may
275 determine localization of the lesions elsewhere e.g. on face, neck or feet. Systemic
276 involvement and/or fatal outcome of human CPXV infections have been reported only
277 for immune-comprised individuals thus far (Czerny et al., 1991; Pelkonen et al.,
278 2003). Infections of humans may become more numerous due to the lack of an
279 absent or adequate immune status of the population because of the abrogated, but
280 cross-protective smallpox vaccination on the 1980ies.

281 Reservoir of cowpox virus

282 Like all above mentioned animal host species (cows, cats, elephants, etc) humans
283 are default hosts of CPXV, while several wild rodent species act as a reservoir for
284 CPXV (table 3). Serological and PCR data from Great Britain, Norway, Sweden,
285 Finland, Russia and Germany confirmed that different vole species, mice and gerbils
286 (see table 3) serve as a natural reservoir for CPXV. In recent years transmission by
287 (sometimes also cuddly) rats to other host species including humans “emerged” (e.g.
288 Wolfs et al., 2002; Martina et al., 2006; Kurth et al., 2008). Consequently, these
289 reports lead to the assumption that this particular reservoir may have been
290 underestimated but that many rodent species may serve as a reservoir for CPXV.

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

302

303 **Parapoxviruses and yatapoxviruses**

304 Parapoxviruses form a divergent group of viruses with zoonotic parapoxvirus (PPV)
305 infections mainly reported from persons with close contact to sheeps and cattle.
306 Infections are usually benign and only local lesions develop mostly on the hands. The
307 majority of human cases are caused by Orf virus (ORFV). In flocks the incidence can
308 be as high as 90%, but the mortality is usually low. Pseudocowpoxvirus (PCPV, syn.
309 Milker's nodule virus, paravaccinia virus), bovine popular stomatitis virus (BPSV, syn.
310 Bovine popular stomatitis virus) and parapoxvirus of red deer in New Zealand (PVNZ)
311 are also listed as PPV species. In the last decade infections of different seal species
312 (e.g. *Callorhinus ursinus*, *Phoca virulina*, *Halichoerus grypus*, *Leptonychotes*
313 *weddellii*), sea lions (e.g. *Zaophus californianus*, *Otaria bryonia*), camels (*Camelus*
314 *dromedaries*), Japanese serow (*Capricornis crispus*), and further deer species (e.g.
315 *Cervus nippon centralis*, *Rangifer tarandus tarandus*) with parapox viruses were
316 described with a yet unclear zoonotic potential (Büttner & Rhiza, 2002; Mercer et al.,
317 2007; see table 1).

318 In comparison to the worldwide occurrence of parapoxvirus infections, yatapox virus
319 infection is a rare exotic, mild disease mostly characterized by vesicular skin lesions
320 in humans (Tanapox virus) or monkeys (Yaba-like disease virus), or focalized
321 epidermal histiocytomas (Yaba monkey tumor virus). Natural infections are reported
322 from equatorial Africa, i.e. Kenia, Kongo. So far, only around a dozen case reports
323 from monkeys and humans have been published (e.g. Stich et al., 2002; Dhar et al.,
324 2004). The disease may play a minor role in primates kept in zoos, e.g. African green
325 monkey (*Cercopithecus aethiops*), baboons (*Papio cynocephalus anubis*, *Papio*
326 *papio*), rhesus monkeys (*Mucaca mulatta*), bonnet (*Mucaca radiata*) and Asiatic
327 cynomolgus (*Macaca iris*). Although the speed of disease progression of the various
328 para- and yatapox viruses varies considerably, the direct contact to a pox lesion or an
329 immediate contact to contaminated items with skin is thought to be required for an
330 infection. For more indepth reviews on zoonotic aspects of parapoxviruses and
331 yatapoxviruses the respective chapters of the recently published book "Poxviruses"
332 by Mercer et al., 2007 are recommended.

333

334 **Diagnosis**

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

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

349 Differential diagnoses of poxviral infections in humans include the following: MPXV
350 infections can be mistaken by chickenpox infections as clinical symptoms are almost
351 identical. At the onset of diseases caused by most poxvirus infections when
352 erythema, edema, papules or nodules with blisters appear e.g. Herpes simplex virus-
353 1 and -2, beta-hemolysing *Streptococcus* of group A, *Staphylococcus aureus*,
354 *Haemophilus influenzae*, *Neisseria pneumoniae*, *Bartonella henselae* should be
355 concerned. In the later course of the disease, i.e. if ulcers and crusts are present,
356 agents such as *Bacillus anthracis*, *Francisella tularensis* or *Treponema pallidum* also
357 should be taken into account. Bacterial and fungal secondary infections have been
358 reported for human and animal hosts.

359 Occupational risk for poxvirus infections has been reported e.g. for cow workers
360 (PPV), health care workers (VACV), animal traders (MPXV) and animal keepers
361 (MPXV, CPXV), (Reynolds et al., 2007; Croft et al., 2003; Juncker-Voss et al., 2004;
362 Trindade et al., 2007a; Kurth et al., 2008). For monkeypox the CDC has published
363 interim guidelines for veterinarians and animal traders
364 (<http://www.cdc.gov/ncidod/monkeypox/pet.htm>).

365

366 **Conflict of interest statement**

367 None.

368

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538

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

Genus and virus species	Geographical distribution	Host	Reservoir
<i>Orthopoxvirus</i>			
<i>Variola virus</i>	eradicated	human	none
<i>Monkeypox virus</i>	Africa, (USA) ²	human, primates (see table 2)	squirrels, dormice, Gambian giant rat, hedge hog, Jerboa, opossum, woodchuck (see table 2)
<i>Cowpox virus</i>	Western Eurasia	human, cat, cow, elephant and zoo animals (see table 3)	rodents (see table 3)
<i>Vaccinia virus</i> ¹ (~ <i>Buffalopox</i>)	worldwide	humans, cattle, buffalos, rabbit	Most likely rodents
<i>Parapoxvirus</i>			
<i>Orf virus (contagious ectyima, contagious pustular dermatitis)</i>	worldwide	humans, sheep, goat, artiodactyla, ruminant	Unknown?
<i>Bovine papular stomatitis virus</i>	worldwide	humans, cattle	Unknown?
<i>Pseudocowpox virus (paravaccinia, melkers nodule)</i>	worldwide	humans, cattle	Unknown?
<i>Parapox virus of seals</i>	worldwide	humans, seals	Unknown?
<i>Parapox virus of reindeer</i>	Finland	humans, reindeer	Unknown?
<i>Molluscipoxvirus</i>			
<i>Molluscum contagiosum virus</i>	worldwide	humans	no

Yatapoxvirus

<i>Tanapox virus</i>	Africa	humans	Mosquitoes?, rodents?
<i>Yaba-like disease virus</i>	Africa	primates	Unknown?
<i>Yaba monkey tumor virus</i>	Africa	primates	Unknown?

541

542 ¹ Buffalopox virus is a name historically used for VACV infections in buffalos (latin name) and
543 sometimes defined as a sub-species of VACV. Because buffalopox virus is officially not a
544 taxonomically assigned name, we here use the phrase buffalopox for the clinical presentation
545 of a VACV infection in buffalos. ² Import of MPXV to the USA with gambian giant rats.

546

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

Order/Family	Species	Virus isolated	Proven transmission to men
<i>Primates/ Hominidae</i>	chimpanzee (<i>Pan troglodytes</i>)	no	no
	Orangutan (<i>Pongo sp.</i>)	yes	yes
<i>Primates/ Cercopithecidae</i>	cynomolgus monkey (<i>Macaca cynomolgus</i>)	yes	yes
	mona monkey (<i>Cercopithecus mona</i>)	no	no
	black-cheeked white-nosed/ red-tailed monkey (<i>Cercopithecus ascanius</i>)	no	no
	greater spot-nosed monkey (<i>Cercopithecus nictitans</i>)	no	no
	lesser spot-nosed monkey (<i>Cercopithecus petaurista</i>)	no	no
	grivet (<i>Cercopithecus aethiops</i>)	no	no
	Allen's swamp monkey (<i>Allenopithecus nigroviridis</i>)	no	no
	Tana river/agile/crested mangabey (<i>Cercocebus galeritus</i>)	no	no
	<i>Primates/ Colobinae</i>	Western red colobus (<i>Piliocolobus badius</i>)	no
<i>Artiodactyla/ Suidae</i>	domestic pig (<i>Sus scrofa</i>)	no	no
<i>Erinaceomorpha/ Erinaceidae</i>	African hedge hog (<i>Atelerix spp.</i>),	no*	no
<i>Didelphimorphia/ Didelphidae</i>	gray short-tailed opossum (<i>Monodelphis domestica</i>)	no*	no
	Southern/common opossum (<i>Didelphis marsupialis</i>)	no*	no
	<i>Rodentia/ Sciuridae</i>	rope squirrel (<i>Funisciurus sp.</i>)	yes
	ribboned rope squirrel (<i>Funisciurus lemniscatus</i>)	no	no
	Thomas's rope Squirrel (<i>Funisciurus anerythrus</i>)	yes	no
	Lady Burton's rope squirrel (<i>Funisciurus ilsabella</i>)	no	no
	Congo rope squirrel (<i>Funisciurus congicus</i>)	no	no
	Gambian sun squirrel (<i>Heliosciurus gambianus</i>)	no	no
	Red-legged sun squirrel (<i>Heliosciurus rufobrachium</i>)	no	no
	Prairie dogs (<i>Cynomys sp.</i>)	yes	yes
	black-tailed prairie dog (<i>Cynomys ludovicianus</i>)	no*	no
	woodchuck (<i>Marmota monax</i>)	no*	no
<i>Rodentia/ Gliridae</i>	dormouse (<i>Graphiurus spp.</i>)	yes	
<i>Rodentia/ Hystricidae</i>	African brush-tailed porcupine (<i>Atherurus africanus</i>)	no	no
	<i>Rodentia/ Nesomyidae</i>	Gambian giant rat (<i>Cricetomys</i>)	yes

	sp.)		
	Emin's pouched rat/Gambian rat (<i>Cricetomys emini</i>)	no	no
<i>Rodentia/ Dipodidae</i>	Jerboa (<i>Jaculus spp.</i>)	no*	no
<i>Macroscelidea/Macroscelididae</i>	Four-toed elephant shrew/Sengi (<i>Petrodromus tetradactylus</i>)	no	no

549

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550 **Table 3: Different hosts of cowpox virus as demonstrated by serological**
 551 **evidence and/or virus isolation**

Order/Family	Species	Virus isolated	Proven transmission to men
<i>Primates/ Cercopithecidae</i>	Barbary macaque (<i>Macaca sylvanus</i>)	no	no
<i>Primates/ Callitrichidae</i>	marmoset (<i>Callithrix jacchus</i>)	yes	no
<i>Carnivora/Felidae</i>	cat (<i>Felis sylvestris f. Catus</i>)	yes	yes
	cheetah (<i>Acinonyx jubatus</i>)	yes	yes
	lynx (<i>Lynx lynx</i>)		no
	lion (<i>Panthera leo</i>)	yes	no
	black panther (<i>Panthera pardus</i>)	yes	no
	ocelot (<i>Felis pardalis</i>)	yes	no
	jaguar (<i>Felis onca</i>)	yes	no
	puma (<i>Felis concolor</i>)	yes	no
	far eastern cat (<i>Felis bengalis</i>)		no
	<i>Carnivora/Herpestidae</i>	banded mongoose (<i>Mungos mungo</i>)	yes
<i>Carnivora/ Canidae</i>	dog (<i>Canis lupus familiaris</i>)	yes	no
	fox (<i>Vulpes vulpes</i>)	no	no
	arctic fox (<i>Alopex lagopus</i>)	no	no
	stone marten (<i>Martes martes</i>)	no	no
<i>Carnivora/ Mustelidae</i>	stone marten (<i>Martes martes</i>)	no	no
<i>Carnivora/ Ailuridae</i>	bearcat (<i>Ailurus fulgens</i>)	yes	no
<i>Artiodactyla/ Suidae</i>	wild boar (<i>Sus scrofa</i>)	no	no
<i>Artiodactyla/ Giraffidae</i>	okapi (<i>Okapia johnstoni</i>)	yes	no
<i>Artiodactyla/ Bovidae</i>	cow (<i>Bos taurus</i>)	yes	yes
<i>Artiodactyla/ Camelidae</i>	lama (<i>Lama glama pacos</i>)	no	no
<i>Perissodactyla/ Equidae</i>	horse (<i>Equus caballus</i>)	yes	no
<i>Perissodactyla/ Rhinocerotidae</i>	black rhinoceros (<i>Diceros bicornis</i>)	yes	no
	white rhinoceros (<i>Ceratotherium s. simum</i>)	yes	no
<i>Perissodactyla/ Tapiridae</i>	tapir (<i>Tapirus indicus</i>)	yes	no
<i>Proboscidea/ Elephantidae</i>	Asian elephant (<i>Elephas maximus</i>)	yes	yes
	African elephant (<i>Loxodonta africana</i>)	yes	no
<i>Pilosa/ Myrmecophagidae</i>	anteaters (<i>Myrmecophaga tridactyla</i>)	no	no
<i>Rodentia/ Castoridae</i>	beaver (<i>Castor fibor canadensis</i>)	yes	no
<i>Rodentia/Arvicolidae</i>	bank voles (<i>Myodes glareolus</i>)	no	no
	gray-sided vole (<i>Clethrionomys. rufocanus</i>)	no	no
	red-backed voles (<i>C. rutilus</i>)	no	no
	field vole (<i>Microtus agrestis</i>)	yes	no
	root vole (<i>Microtus oeconomus</i>)	no	no
	wood mice (<i>Apodemus sylvaticus</i>)	no	no
	yellow-necked mice (<i>Apodemus flavicollis</i>)	no	no
<i>Rodentia/Muridae</i>	house mice (<i>Mus musculus</i>)	no	no
	common rat (<i>Rattus norvegicus</i>)	yes	yes
	giant gerbil (<i>Rhombomys opimus</i>)	yes	no
	gerbil (<i>Meriones lybicus</i>)	yes	no
	ground squirrel (<i>Citellus fulvus</i>)	no	no
<i>Rodentia/ Caviidae</i>	Patagonian cavy (<i>Dolichotis patagonum</i>)	no	no
<i>Insectivora/ Soricidae</i>	common shrew (<i>Sorex araneus</i>)	no	no

552