*Review*

# Recent insights into Bovine Papillomavirus

## Freitas, A. C.*, Silva M. A. R., Jesus, A. L. S., Mariz, F. C., Cordeiro, M. N., Albuquerque, B. M. F. and Batista, M. V. A

Laboratory of Molecular Studies and Experimental Therapy, Department of Genetics, Center for Biological Sciences, Federal University of Pernambuco, Recife, PE, Brazil.

**Bovine papillomaviruses (BPV) are double-stranded DNA viruses that infect the cutaneous and mucosal epithelia inducing hyperplasic lesions in cattle. BPV is the etiologic agent of the papillomatosis and neoplasia of the upper gastrointestinal tract and urinary bladder. The benign and malignant tumors caused by BPV are emergent diseases important for beef and dairy cattle in the world. Although BPV associated tumors have veterinary and agricultural relevance, they have also been studied as a relevant model of human papillomavirus (HPV). Recent studies in BPV biology have shown a great diversity of BPV types and new putative BPV types infecting and co-infecting the herd in several parts of the world. This review will briefly summarize the genomes and structure of BPV and the bovine papillomatosis; will describe in greater detail the genotypic diversity, BPV cross-species infection, relevant aspects of BPV and co-infection and its possible routes of transmission. These new approaches about BPV may be very useful to understand the oncogenic potential of the virus, the relationship between virus and co-factors, and the development of anti-viral vaccines.**

**Key words:** Bovine papillomavirus, co-infection, virus transmission, BPV diversity.

## INTRODUCTION

Papillomaviruses (PVs) are a diverse group of small, nonenveloped, circular double-stranded DNA viruses that occur in a broad range of animal species belonging to the amniotes, including humans (Antonsson and Hansson, 2002). Bovine papillomavirus induces diseases of considerable veterinary importance in farm animals, but has also an enormous value as an in vivo model for HPV. They infect the epithelia of vertebrates, where they can cause neoplasias or persist asymptomatically. After being assorted in the old family Papovaviridae, PVs were re-designated as a distinct family, Papillomaviridae (van Regenmortel et al., 2000). BPVs are a heterogeneous group of epitheliotropic viruses that recognize bovines as its classical host. Twelve BPV types have been characterized and classified into three genera: *Deltapapillomavirus* (BPV-1 and -2), *Epsilonpapillomavirus* (BPV-5 and -8) and *Xipapillomavirus* (BPV-3, -4, -6, -9, -10, -11 and -12), and

an as yet unassigned PV genus (BPV-7) (Bernard et al., 2010; Hatama et al., 2011; Zhu et al., 2011). The bovine papillomatosis is an important disease leading to economic depreciation of animals, deterioration of the appearance and of the animal leather. The lesions may progress to cancer due to the synergistic action of genetic or environmental co-factors (Borzacchiello and Roperto, 2008; Leal et al., 2003). Recent insights into BPV biology open new fields of discussion about co-infection, cross-species infection, and transmission of these viruses.

## GENOMES STRUCTURE OF BOVINE PAPILLOMAVIRUS

BPV genomes comprise nearly 8 Kb, which includes a long control region (LCR), early (E) and Late (L) genes (Figure 1). The LCR (about 500-1000 nucleotides) contains transcriptional regulatory sequences and the replication origin (Munger and Howley, 2002).
    There are six early genes, all of them expressed
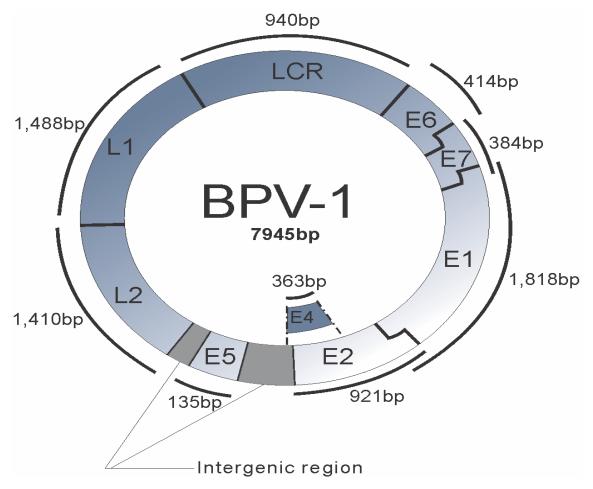
*Corresponding author. E-mail: acf_ufpe@yahoo.com.br.

**Figure 1.** Genomic organization of BPV-1 showing the genomic positions of viral genes E6, E7, E1, E2, E4, E5, L2, L1, and the long control region (LCR) between L1 and E6 genes; as well as the intergenic regions between E2 and E5, and between E5 and L2.

according to the viral life cycle into the host cell. The E1 protein has helicase activity and plays its role on the viral replication (Lambert, 1991). The E2 gene product is responsible for recognition and ligation to the replication origin and, furthermore, it has mitotic chromosome binding activity in order to ensure equal distribution of viral episomes among daughter-cells (Baxter et al., 2005). The E4 gene, completely overlapping E2 gene but in a different reading frame, produces a small protein profusely found in keratinocytes cytoplasm during productive replication (Anderson et al., 1997). Three early proteins are necessary for BPV-mediated carcinogenic process, so, called oncoproteins: E5, E6 and E7 (Nasir and Campo, 2008). E5 is a membrane-associated hydrophobic protein, which plays a role on disrupting cellular growth control. BPV E6 protein is known to have a multitude of binding partners and activities on the virus life cycle. In *Xipapillomavirus*, E6 gene is replaced by an E5-like gene, which was initially defined as E8.

Nevertheless, the comprehension that most (although not all) of the functions of this protein are shared with

BPV-1 E5, prompted its redefinition as E5 (Campo, 2006). The E7 protein appears to cooperate with E5 and E6 for cellular transformation, whose production with the two others oncoproteins increases the transformation efficiency (Bohl et al., 2001).

The viral capsid structure is constituted by two proteins (Modis et al., 2002; Xu et al., 2006) encoded by the late genes in viral genomes. The L1 gene is useful for classification and construction of phylogenetic trees (Bernard, 2005). The capsid is formed by 360 copies of L1 protein, organized as 72 capsomers (pentameric assembled), and 12 copies of L2 protein. Although being present in less number, L2 minor capsid protein is necessary for viral morphogenesis (Modis et al., 2002).

## BPV DIVERSITY

The present PV diversity can be explained by multiple evolutionary mechanisms (Gottschling et al., 2007). Virus host-divergence is an important evolutionary force,

however this force solely cannot explain the evolution of PVs and their diversity, thus alternative mechanisms such as within-host virus duplication, recombination, viral sorting, or viral adaptation after a host switch, may therefore contribute considerably to explain the PV diversification (Shah et al., 2010; Gottschiling et al, 2011).

Although it is not very clear how these evolutionary mechanisms act on PV diversity, several robust methods have been used. Gottschling et al. (2007) used a rigorous phylogenetic approach, which took into consideration the choice of appropriate outgroups, as well as the assessment of confidence values of internal nodes. A robust study has used the method of importance sampling to Bayesian divergence time estimation, which indicates prior divergence of at least 6 PVs lineages associated with an ancestral mammalian host (Shah et al., 2010). Gottschiling et al, (2011) used different statistical approaches to assess topological and branch-length congruence, evidencing the importance of alternative mechanisms other then codivergence. Another statistical approach based on entropy was used to assess the evolution of PVs, showing that hot spots in the genome could be used as markers in order to infer PV phylogeny (Batista et al., 2011). These robust phylogenetic analyses provide the basis for contemporary classification of PVs, which is very important for any medical and veterinary researches.

The understanding of PV diversity is limited, probably underestimated. As there are more than 150 sequenced HPV genomes, less than 50 non-human papillomavirus species have been isolated and sequenced. So, more new PV types should be sequenced to increase our knowledge about PV evolution. The diversity of subtypes and variants could show a more detailed and refined scenario of PV diversification, increasing insights into the representativeness of each PV type. When it comes to BPV, 12 types are currently well described and about 14 new putative types were isolated (Antonsson and Hansson, 2002; Ogawa et al., 2004; Campo, 2006; Ogawa et al., 2007; Tomita et al., 2007; Claus et al., 2008; Hatama et al., 2008; 2011; Zhu et al., 2011).

In phylogenetic analysis, BPVs are found in at least three distantly related lineages. First, BPV-1, BPV-2, BPV-5 and BPV-8 form a paraphyletic group with OvPV-1 and OvPV-2, which infects a close related host. Other PVs that infect Artiodactyla are also close relatives of those BPVs. However, this group is clustered together with equine and canine PVs. Second, BPV-3, BPV-4, BPV-6, BPV-9, BPV-10, BPV-11 and BPV-12 are grouped together with caprine PV (ChPV-1). This group is related with a large cluster that involves human, canine and rodent PVs. BPV-7, an unclassified PV, has an uncertain phylogenetic position, which makes it difficult to infer its relatedness to other PVs.

Therefore, all this diversity found in PVs that infect one host (*Bos taurus*) is a case of evolutionary incongruence

between host and PV phylogeny, indicating that co-divergence alone cannot explain the PV diversity (Gottschling et al., 2007, 2011; Shah et al., 2010).

Some conflicting phylogenetic positions of types within *Xipapillomavirus*, which includes some BPV types, have been shown when analyzing early or late genes phylogenies (García-Vallvé et al., 2005; Köhler et al., 2011). In general, the topological inconsistency between early and late genes phylogenies have been explained with ancient recombination events (Gottschling et al., 2007; Shah et al., 2010). This also could be the explanation for the contradicting positions of BPVs within *Xipapillomavirus*. For BPVs, at least three lineages seem to originate the currently known types. These lineages probably passed through a prior divergence process preceding the host divergence. This could also explain the proximity of BPVs to PVs that infect distantly related hosts. In addition, zoonotic transmission of PVs is rare event but it occurs in BPVs as they were found in zebras, horses and buffaloes (Silvestre et al., 2009; van Dyk et al., 2009; Bogaert et al., 2010a). Other evolutionary mechanisms could be associated with BPV diversification, however sampling is still a limiting factor.

## BPV DETECTION AND DISTRIBUTION

BPV DNA is detected by a variety of polymerase chain reaction (PCR)-based techniques. These PCRs are based frequently on the detection of one or two BPV types using degenerated or type-specific primers. Genotyping is performed either by real-time detection (Rai et al., 2011) or by sequence analysis (Brandt et al., 2008) or restriction fragment length polymorphism (RFLP) analyses (Carr et al., 2001) of the generated PCR fragments. Consensus primers capable of identifying potentially more than two BPV types have also been described (Ogawa et al., 2004). Besides, PCR assays, designed originally for the detection of human papillomaviruses have been used to genotype different BPV types (Antonsson and Hansson, 2002; Ogawa et al., 2004). PCR assays using degenerate primers that amplify partial fragments of the L1 gene, followed by sequencing, have suggested the existence of numerous yet uncharacterized BPV types in cattle herds from diverse geographical regions. Using the primers FAP59/FAP64 and MY09/MY11, 12 putative new BPV types were detected in teat skin warts and healthy teat skin of cattle from Japan and Sweden (Antonsson and Hansson, 2002; Ogawa et al., 2004).

Bovine papillomavirus has been widely found in cattle worldwide. Cases have been reported in the incidence of BPV in cattle in Europe, America, Asia and Oceania. BPV-1, -6, -8 and -10 were found in bovine warts from a German cowshed (Schmitt et al., 2010). In Japan, heifers were found to have benign teat tumors causing by BPV-6 (Maeda et al., 2007). In another work, Ogawa et al. (2004)

detected BPV-1, -3, -5 and -6 in papilloma specimens. Bovine cutaneous warts were reported from India and identified as BPV types 1 and 2 (Singh et al., 2009; Pangty et al., 2010) and recently Rai et al. (2011) identified BPV-10 in teat warts from cattle at a dairy farm in India. Cattle from Brazil have also been investigated for the presence of BPV. It was identified BPV-1, -2, -6 and -8 in skin warts of cattle from southern Brazil (Claus et al., 2007; Sá e Silva et al., 2010). Results from our group, in northeastern Brazil, also revealed the presence of ten different types of BPV in the samples, with the exception of BPV-7 (Carvalho et al., in press).

As considered before, BPV is also associated with cancer in cattle. BPV-4 infection and associated tumors of upper GI tract have been found in Brazil, the Nasampolai Valley of Kenya, Western Highlands of Scotland and in southern Italy (Jarrett et al., 1978; Borzacchiello et al., 2003). Field cases of urinary bladder cancer in cattle associated with BPV-1 and -2 infections were reported in continental Europe, Azores Islands, some regions of Kenya, Brazil, New Zealand, India and China (Borzacchiello and Roperto, 2008).

A similar investigation revealed notable diversity among BPV types detected in papillomas of four cattle herds in southern Brazil. The study identified four putative new BPV types designated as BPV/BR-UEL2 to BPV/BR-UEL5 (Claus et al., 2008). Phylogenetic analysis using complete L1 ORF sequences revealed that the one of the isolates was similar with BPV-4 (78%), which suggested its classification in the genus *Xipapillomavirus* (Lunardi et al., 2010).

In a work of our group it was also detect possible new types and variants in samples from herd in northeastern Brazil, in which sequence analyses indicated the presence of two isolates (BPV/UFPE01 and BPV/UFPE02) of a putative new BPV-11 subtype (unpublished data). These two novel isolates are also closely related to BPV-4, and to the strains BPV/BR-UEL2 and BPV/BR-UEL3 described by Claus et al. (2008). Currently, the group continues the analysis of new BPV DNA sequences from cutaneous warts with very promising results for the identification of new types of BPV in Brazilian cattle.

## BOVINE PAPILLOMATOSIS

Bovine papillomatosis is an infectious disease worldwide distributed among herds. The BPV is responsible for this contagious illness, whose remarkable clinical sign is the hiperproliferative lesions, known as papillomas, on cutaneous tissue and mucosa (Campo, 2006). Despite being primarily considered epitheliotropic, BPV DNA has already been isolated from peripheral blood mononuclear cells, milk, urine, seminal fluid and sperm cells of animals infected with BPV-1, BPV-2 and BPV-4 (Carvalho et al., 2003; Yaguiu et al., 2006, 2008; Roperto et al., 2008,

Lindsey et al., 2009).

Similarly to others papillomatosis, it is usually observed the spontaneous regression of lesions, defined as benign proliferative neoplasm (Jelínek and Tachezy, 2005). Many times its importance is not verified by many owners and veterinarians badly clarified. Much more than an esthetic issue, bovine papillomatosis has recently grown in importance due its association with cancer and immunosuppression conditions (Campo, 2002). This infection, according to the viral type and environmental co-factors, causes distressing symptoms in cattle, as cutaneous fribropapillomas (BPV-1, and -2), cancer of the upper gastrointestinal tract (BPV-4), papillomatosis of teats and udder (BPV-1, -5, -6, -9 and 10) and penis (BPV-1) and cancer of the urinary bladder (BPV-1 and -2) and cutaneous papillomas (BPV-8) (Borzacchiello and Roperto, 2008) (Figure 2). Even the benign progression demands attention, once hyperplasic lesions may depreciate the pelt in affected animals; when located in the udder, it may lead to secondary infections and lactation problems. In fact, Campo (2006) related several economic consequences, as cows with teat papillomas cannot be milked, young calves cannot suckle, and often the peduncolated papillomas snap off, the sites become infected and mastitis may ensue with distortion of the milk canals. Animals can also develop extensive papillomas in the upper gastrointestinal tract and, consequently, present difficulty to feed and breathe, resulting in a debilitated animal that may come to death (Campo, 1997).

At the moment, there is no vaccine or effective treatment for the control of papillomatosis. There are few BPV treatments available with levels of success varying between 15-50%. However, it was evident the economic unavailability to repeat the treatment in animals that did not recover after the first therapeutic intervention (Silva et al., 2004).

## BPV AND CO-INFECTION

Some reports describe the occurrence of co-infection with different types of BPV worldwide. In Japan, Ogawa et al. (2004) verified the presence of BPV in up to four BPV types and putative new BPV types in the same papilloma in the Japanese herd. In Brazil, the simultaneous presence of BPV-1 and -2 was detected in the same lesion (Yaguiu et al., 2006, 2008; Lindsey et al., 2009). Also, it was found five different combination of multiple BPV infection in cattle (Claus et al., 2009). Co-infection with BPV-1 and -2 was described in India (Leishangthem et al., 2008; Pangty et al., 2010) and co-infection with BPV-1 and -11 was assessed using a multiplex BPV genotyping assay in bovines in Germany (Schmitt et al., 2010) and in Brazil using specific BPV primers (Carvalho et al., in press).
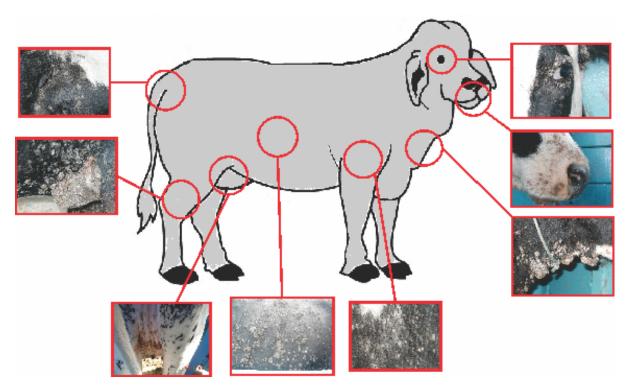
Co-infection of FeSarPV, a new putative PV type

**Figure 2.** Schematic view of bovine papillomatosis in different sites of the cow.

related to Delta-PVs, and BPV-2 was described in New Zealand (Munday and Knight, 2010) and Brazil (Silva et al., unpublished data). In healthy cattle, the papillomas normally regress, but in cattle which have been fed on bracken fern (*Pteridium aquilinum*), there is a good correlation between persistent papillomatosis and cancer (Campo, 1997). However, the persistence of skin warts has been seen in a large number of animals (Claus et al., 2009). As several animals are constantly affected with warts in diverse body parts, it could be consequence of co-infection, which could lead to fall of immune response and prevent the regression of the lesions.

During several years, most of the first six well characterized BPVs have been described as causative agents of specific lesions in distinct body sites of bovines: BPV-1 has caused teat frond and penile fibropapillomas; BPV-2 has been described as the agent of common warts and esophageal fibropapillomas; BPV-3 and -8 in the epithelial papillomas of the skin; BPV-4 has been described as the agent of papillomas of the alimentary canal, showing specificity to the mucous epithelium; BPV-5 has caused rice grain fibropapillomas of the udder, and BPV-6 has been isolated from teat frond papillomas, BPV-9 and -10 has been associated to epithelial squamous papillomas of the udder (Campo, 1997; Borzacchiello and Roperto, 2008). However, in the late years, a diversity of multiple bovine papillomaviral infection has been described in bovine and other mammals (Ogawa et al., 2004; Bogaert et al., 2008; Claus et al., 2009; van Dyk et al., 2011) suggesting that certain viral types are not restricted as previously thought. Claus et al. (2009) observed the occurrence of several BPV types in a specific anatomical region; the detection of the same viral type in distinct body sites and determining papillomas with diverse gross aspects; and lesions with similar morphological characteristics caused by distinct papillomavirus.

Besides cutaneous warts lesions in cattle, the presence of more than one putative new BPV type was also observed in the normal skin (Ogawa et al., 2004). The simultaneous presence of BPV-1 and -2 was demonstrated in others bovine tissue such as blood and reproductive cells (Yaguiu et al., 2006, 2008; Diniz et al., 2009; Lindsey et al., 2009). BPV-1 and -2 was found co-infecting giraffe (van Dyk et al., 2011), zebra (van Dyk et al., 2009) and horse (Bogaert et al., 2008).

According to Schmitt et al. (2010), the occurrence of diverse co-infection by BPV in a single sample suggests that natural competition of different BPV types may not occur on the skin.

However, it is not clear if all BPV types founded in the lesion are transcriptionally active. Detection of viruses in apparently latency may be a result of evasion from the immune system (Schmitt et al., 2010). Nonetheless, the distribution of BPV types appeared to resemble the situation known from skin HPV types, where co-infections of more than 10 genotypes are detected frequently at very low copy numbers (Antonsson et al., 2000). In preliminary data obtained by our research group, we found very low copy number of BPV in cutaneous lesion

co-infected by several viral types (unpublished data).

## TRANSMISSION OF BPV

Currently, little is known about how the disease is transmitted between animals. About this important question, it is known that confined populations are more vulnerable because virus dissemination may occur by direct (animal to animal) or indirect (contaminated objects) contact (Hama et al., 1988; Nasir and Campo, 2008). Besides the established skin–skin pathway, another via like arthropod vector and vertical trans-mission has been suggested (Freitas et al., 2003; Finlay et al., 2009). However these alternatives via of transmission might be less efficient (Bravo et al., 2010).

The increasing interest of studying BPV in the blood revealed this tissue as a source of spreading to BPV through non-epithelial tissues and fluids (Stocco dos Santos et al., 1998; Freitas et al., 2007). This hypothesis may be corroborated by the detection of BPV in different tissues and cells, including reproductive sites as oocytes, ovary, uterus, cumulus cells, and uterine lavage (Freitas et al., 2003; Yaguiu et al., 2006; Lindsey et al., 2009). The vertical transmission of BPV has been suggested (Stocco dos Santos et al., 1998; Freitas et al., 2003; Yaguiu et al., 2008). Also for humans, it has been shown that HPV- infected women can transmit the infection to the fetus by transplacental mechanisms (Rombaldi et al., 2008).

The mechanism behind the transmission of BPV to/between no specific hosts is not clear. Recent findings of BPV in epidermis and formation of L1 capsomers of equine sarcoid and active-BPV in normal skin of equine (Bogaert et al., 2008; 2010a, b; Brandt et al., 2011) could help explaining the occurrence of equine sarcoid in animals kept far away from any bovine virus source, especially when living in close contact with other affected equids (Brandt et al., 2011). It is believed that flies can be a vector for BPV and transmit the virus between bovine and horses (Nasir and Campo, 2008; Finlay et al., 2009). However, there is no further information about this virus–vector– host system. The zoonotic potential and the medical implications for the corresponding transmission route need to be explored (Bravo et al., 2010). Alternatively, BPV infection may be transmitted via stable management practices, or passed into existing wounds from contaminated pasture. Considerably more research is necessary to investigate all of these possibilities (Chambers et al., 2003). The mechanism of transmission of BPV in a cattle herd and to other mammals should be most studied since BPVs are disseminated infecting and co-infecting these animals due to its plasticity.

## BPV AND CROSS-SPECIES INFECTION

Although PVs have been described as specie-specific (Campo, 2006) some PVs infect a variety of hosts. PVs appear to be widespread and have been found in a large number of vertebrate species and are assumed to have co-evolved with their hosts (Bernard, 1994; Antonsson and McMillan, 2006). Strict host specificity of PVs might act as a barrier that prevents close physical contact between different viruses, but a series of PVs infect a variety of phylogenetically distant hosts (Bravo et al., 2010). Virtually all mammalian species are hosts for one or more papillomaviruses (Sundberg et al., 2001). BPV can infect cattle but also infect close relatives of cattle such as buffalo (Silvestre et al., 2009; Pangty et al., 2010) and giraffe (van Dyk et al., 2011) causing fibropapillomas and bladder lesions (Pathania et al., 2011). Moreover, these viruses naturally infect more distantly related species, such as tapirs (Kidney and Berrocal, 2008), horses (Bogaert et al., 2008), sable antelope (van Dyk et al., 2011), and zebras living either in zoos (Löhr et al., 2005) or in the wild (van Dyk et al., 2009) causing sarcoids, and fibrosarcomas when inoculated into rodents (Robl and Oslon, 1968). Also, a variant of BPV-8 can induce papillomas in Bison (Literak et al., 2006) (Figure 3).

FeSarPV, primarily identified feline sarcoid, was verified in bovine fibropapillomas and dermatitis by Munday and Knight, (2010). It has been suggested that FeSarPV is a bovine PV causing a non-productive cross-infection in felines as well as BPV-1 and BPV-2 causes sarcoids in equids. Recently, it was found L1 capsomers in epidermis of equine with sarcoid suggesting a productive infection by BPV (Brandt et al., 2011). A newly proposed BPV type BRUEL- 4 (Claus et al., 2008) was identified in a sarcoid tumor of a horse, revealing a new viral type associated with equine sarcoid (Sá e Silva et al., 2010).

The ability of BPV-1 to infect related hosts can be a result of human domestication of cattle and horses or a phenotypic acquisition driven by vector-mediated interspecies transmission (Finlay et al., 2009; Gottschling et al., 2011). Thus, ecological changes happened concomitantly in the different hosts may have increased their susceptibility to BPV cross-infection and/or have simply increased the frequency of physical contact between them to grant BPV improved access to a potential new host (Gottschling et al., 2011).

## CONCLUSION

Bovine papillomavirus is a group of viruses extensively studied in the last years. BPV has always been considered as an excellent experimental model to investigate HPV infection and carcinogenesis. It is also useful to understand the oncogenic potential of the virus, the relationship between virus and co-factors, and the development of anti-viral vaccines. In this review, we broach new insights into the mechanisms of BPV co-infection, cross-species infection and transmission.
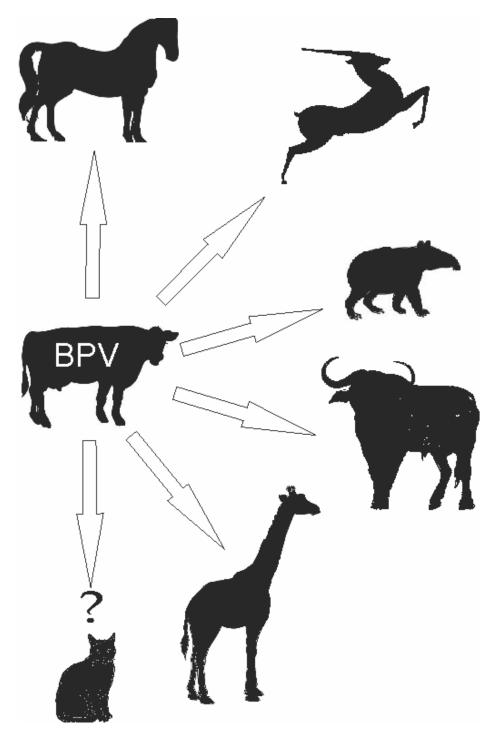
**Figure 3.** Schematic presentation of cross-infection caused by BPV. BPV DNA was found in close and distant related hosts: horse, sable antelope, tapir, buffalo, giraffe and possible cat.

New aspects involving the mechanisms of BPV transmission and cross-species infection have broken some paradigms about these viruses. The BPV status as an epitheliotropic and species-specific viruses can no longer be seen that way. The heterologous BPV infection has been consistently documented by several research groups worldwide, as well as the evidence of the presence of the virus in non-epithelial tissues.

The co-infection by multiple BPV has also generated interesting discussions. The occurrence of several BPV types in a specific anatomical region suggests that both multiple papillomavirus infections and high viral diversity can be frequent in cattle. The identification of multiple BPV infections may contribute to the understanding of the

epidemiological, clinical, and immunological features of cutaneous papillomatosis in cattle. Particularly for the immunological approach, this multiple infection brings important implications when is considered immunization strategies to eradicate papillomatosis, since the introduction of vaccines against a single BPV type may contribute to the spread of other genotypes able to cause skin lesions with similar morphological characteristics in cattle.

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