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A Combination of Chemotherapy and Autogenous Vaccine for Control of Bovine Papillomatosis in Cattle

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ABSTRACT

The present study was conducted during the period from July, 2023 to January, 2024. Two clinical cases of cattle were reported with cutaneous papillomas, one near right umbilical region and another over the right hind teat of cattle. Both the animals were treated with a protocol designed such that it can regulate the secondary bacterial infection, speedy recovery of integument system and enhance the immune response for complete regression of the warts. The innate immune responses of infected animals were augmented with inactivated pathogen associated molecular patterns (PAMPs) as autogenous vaccine candidate. The warts were surgically excised, triturated in sterile PBS, inactivated with 0.5% formaline and prepared the autogenous vaccine. The sterility test of vaccine revealed that the vaccine was free from bacterial and fungal contaminants. The chemotherapy includes the use of drugs Thuja ointment, Inj.Enrofloxacin, Inj.Avil and Inj.Anthiomaline. The dose of the vaccine was 1 ml 20 kg^{-1} b.wt. subcutaneously and given at weekly intervals for a period of 4 weeks. It was observed that the treatment protocol was successfully effective and regression of warts was noticed from 2nd week onwards. By end of 4th week a complete recovery of the wart infected area was noticed with a black scar left behind. The formalin inactivated autogenous vaccine was effective, and applied for control of bovine papillomavirus infection in cattle with combination of chemotherapeutic drugs resulted in early regression of warts.

KEYWORDS: Autogenous vaccine, warts, bovine papillomavirus, immune response

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1. INTRODUCTION

Bovine papillomatosis or warts is a common viral disease of cattle which is highly infectious, manifest as a neoplastic like growth on the integument system (Hauck, 2008). The Warts develop as a benign exophytic proliferative lesions, in some instances can progress to malignant form that induce systemic infection (Borzacchiello and Roperto, 2008; Bertagnolli et al., 2020). The disease is prevalent in cattle globally, most commonly observed in dairy cattle than in other domestic animal. The incidence of disease is highest in calves and yearlings when compared with the adult animals (Salib and Farghali, 2011). It can directly and indirectly cause economic losses due to reduction in milk production, poor quality meat, animal products, medicine expenditure, depreciation of animal's value and reduced hide quality (Freitas et al., 2011).

The bovine cutaneous warts are caused by Bovine papillomavirus (BPVs), which is classified under the family Papillomaviridae. The genome consists of a double-stranded, circular, DNA (approximately 8kb) (Baker et al., 1987). Based on the sequence analysis of L1 gene sequences, the BPVs are classified into five genera, which includes *Delta papillomavirus*, *Xipapillomavirus*, *Epsilon papillomavirus*, *Dyoxi papillomavirs*, and *Dyokappa papillomavirus*. Under each genera several BPV types have been classified and three BPVs (BPV 19, 21 and 29) were not assigned any genera (Van Doorslaer et al., 2013).

The BPVs induce development of cutaneous warts on several parts of the body includes head, neck, eyes, nostrils, oral, tail, udder, genital organs and internal organs such as gastro-intestinal tract etc. (Pathania et al., 2011). However, it is now apparent that multiple different papillomavirus types are present in most bovine papilloma's making it difficult to determine which of these viruses actually caused the papilloma and which represent only a latent virus infection (Batista et al., 2013; Bocaneti et al., 2013). In general, the humoral immune response against BPVs is very poor in the infected hosts, because the virus replication cycle is mainly restricted to the keratinocytes and lack of proper inflammatory response (Campo, 2006). The BPV L1 recombinant capsid protein expressed in bacterial expression system developed promising humoral immune response in calves (Módolo et al., 2017). Recently, bovine papillomavirus type 1-L1 protein was expressed in Baculovirus expression system and developed as Virus like proteins (VLPs), was used as vaccine candidate in mouse model (Vrablikova et al., 2023). The BPV-L1 VLPs are the major targets of research as during recent years, which focussed on immunogenic potential of BPV-L1VLPs (Liu et al., 2012; Jesus et al., 2012; Harnacker et al., 2017; Yang et al., 2021).

The major oncoprotein, E5, of BPV, was shown to negatively regulate the host antiviral innate immune responses (Uhlorn et al., 2020; Guey and Ablasser, 2022). Among the innate immune responses, the cyclic Guanosine monophosphate-Adenosine monophosphate synthase-stimulator of interferon genes (cGAS STING) was identified as potent antiviral effector pathway that sense the abnormal pathological DNA (Chen et al.. 2016; Ablasser and Chen, 2019; Zhao et al., 2021; Fang et al., 2021; Zhang et al., 2019). Many DNA viruses, subvert this pathway to establish infection and induce oncogenesis (Lo Cigno et al., 2020; Luo et al., 2020; Liu et al., 2021; Li K et al., 2019; Oliveira et al., 2020). It was proven that cGAS-STING pathway was impaired by E5 protein of BPV (De Falco et al., 2021 and 2022). Hence, in the present study novel approach was designed such that inactivated pathogen associated molecular patterns of BPV were applied to enhance innate immune responses in BPV infected animals in combination with chemotherapy for control of BPV infections in cattle. The autogenous vaccine developed with wart material and the chemotherapy were considerated for early recovery of BPV infected animals.

2. MATERIALS AND METHODS

Two cattle with bovine papilloma viral infections with presence of cutaneous warts at umbilical region and on teats were presented to the Veterinary Clinical Complex, College of Veterinary Science, Garividi, Vizianagaram district, Andhra Pradesh state, India located at latitude of 18.2892° N, and longitude of 83.5557° E.

2.1. Case details

Case–I: A four year old, Cow with a history of multiple cutaneous nodules at umbilical regions was presented to the Veterinary Clinical Complex, College of Veterinary Science, Garividi, Vizianagaram District, Andhra Pradesh during the month of November, 2023. On clinical examination, the nodules were noticed with varying size, with irregular crusted margins, greyish black and brownish in colour (Figure 1). All other clinical parameters were observed within normal range.

Case–II: Cattle in 2nd lactation was presented to the Veterinary Clinical Complex, College of Veterinary Science, Garividi, Vizianagaram District, Andhra Pradesh in the month of July, 2023 with a history of dark brownish black circular wart like nodules measured approximately 1–1.5 cm over the right hind teat (Figure 2). Except the milk yield and quality of milk, remaining clinical parameters are reported within normal range.

Based on the clinical picture in both cases, preliminarily it was diagnosed as warts due to bovine papilloma viral infections.

Figure 1: Management of warts at umbilical region of the cattle (Case–I)

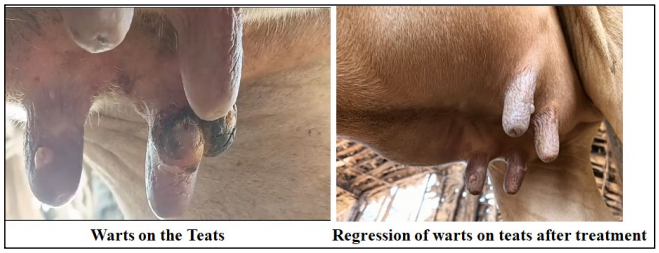

Figure 2: Management of warts on teats of the Cattle (Case–II)

2.2. Sample collection

The warts were excised from both cases following the surgical procedures as sample for further processing. The site was disinfected with 95% ethanol, the wart was excised using a surgical blade and kept in 20 ml of PBS (pH 7.0) added with penicillin and streptomycin. The wart material weighed ~35 grams, was stored at 4°C, until proceed for vaccine preparation.

2.3. Preparation of the inactivated vaccine of BPV

The autogenous vaccine preparation was standardized as per the protocol described by Mayil kumar et al., 2015 with little modifications. Briefly, a twenty grams of the wart material was homogenized with sterile PBS (pH 7.0) and finely triturated using a sterile mortar and pestle until the entire wart turned into a suspension. The homogenized suspension was centrifuged at 5000 rpm for 10 min at 4°C. The supernatant was collected aseptically into a sterile beaker and inactivated by adding formalin solution to a final concentration of 0.5% (v/v). Then penicillin (10000 units)–streptomycin (10 mg) was added 1ml to 100 ml of the vaccine. The suspension was stirred at 4°C for 4 hours on a magnetic stirrer. The inactivated sample was centrifuged at 5000 rpm for 10 minutes, supernatant was collected and stored at 4°C.

2.4. Sterility test

An aliquot of the inactivated vaccine was inoculated onto Brain heart infusion broth, Mac Conkey agar, Blood agar and Sabourad dextrose agar and incubated at 37°C for 48–96 hrs. The inoculated culture media was checked at 12 hrs interval for observable turbidity and bacterial growth by grams staining.

2.5. Treatment

The animal was treated with formalin inactivated BPV autogenous vaccine prepared in the laboratory with a dose of 1 ml 20 kg^{-1} b.wt. subcutaneously. Four consecutive boosters were given at 7 days' interval for a period of 4 weeks. The chemotherapy includes application of Thuja ointment twice daily until recovery, Inj. Enrofloxacin @ 5 mg kg^{-1} bwt IM, Inj.Avil @ 0.5 mg kg^{-1} bwt IM daily for five days and Inj. Anthiomalaline @ 15 ml deep IM on alternative days up to four doses.

3. RESULTS AND DISCUSSION

In bovines the papillomavirus infection causes benign cutaneous fibropapillomas mainly restricted to the superficial layers of the skin keratinocytes (Campo, 2006). These viruses are host specific and several types have been recognized. There is no association between the location of the warts and type of BPV. In general, the treatment options for the control of BPV infections are very poor and largely depend on the chemotherapeutic drugs to manage the inflammation, and secondary bacterial infections. In the present study a traditional approach of formalin inactivated autogenous vaccine of Bovine papilloma virus was applied in combination with regular chemotherapeutic protocols for the control of the infection.

The wart materials excised using sterile surgical blade with minimal bleeding. The excised part of the wound was managed with tincture iodine, followed by application of Thuja ointment (Thuja Occidentalis) twice daily until recovery. The preparation of Thuja occidentalis will helps in speedy recovery from warts. The supportive therapy includes Inj.Enrofloxacin, Inj.Avil and Inj. Anthiomaline. However, the results are inferior than expected under field conditions. The probable reason might be very low level of immune response was developed by the animals against the BPVs. The BPVs lifecycle is mainly restricted to the epidermis, and productive infection is seen in differentiating keratinocytes. The virus genome replication was confined to differentiating keratinocytes of spinous and granular layers, and the mature virion particles released through desquamation of keratinocytes. Because of this strict tropism to keratinocytes and lack of proper inflammatory response, there may be failure of alerting the immune response (Campo, 2006; Stanley, 2006, Zhou et al., 2019). Hence, the present study focussed on enhancing immune response by facilitating the exposure of inactivated bovine papillomavirus particles to immune cells. This was achieved by inactivating the bovine papilloma virus present in the wart material with 0.5% formalin. The homogenized wart

material upon trituration developed a clear suspension and the remnants of the warts were removed by centrifugation. This step was prerequisite that inactivated BPV, otherwise the hidden virus particles deep in the warts might not be properly inactivated, and results in unwanted reactions.

The inactivated autogenous vaccine was checked for sterility by inoculating in BHI broth, Mac Conkey agar and SDA media. No signs of turbidity in BHI broth and growth of bacteria on MacConkey agar was noticed. The vaccine was free from fungi, as evident with absence of growth on SDA media. After passed the sterility test the vaccine was used for control of BPV infection in cattle in combination with chemotherapy.

The autogenous vaccine was injected subcutaneously at the rate of 1 ml 20 kg^{-1} body weight. A total of four doses were given at an interval of 7 days between each dose. The results are encouraging with good progress in regression of the cutaneous warts (Figure 1 and 2). The regression in size of the warts started in the 2nd week, since first dose was given. By end of fourth week, the warts were completely regressed , with mild scars left behing. The efficacy of the BPV autogenous vaccine was reported earlier (Mayilkumar et al., 2014 and Khalid et al., 2020). The warts on teats were progressively regressed by 4th week and by end of 5th week complete regression of warts was reported by Mayilkumar et al., 2014. It took more than 7 weeks for complete regression of the warts around the eye, as reported by Kahlid et al., 2020. However, in our study it took 4 weeks for complete regression (Figure 1 and 2). The probable reason for differences in time of regression between different studies may be variations in individual immune status, level of infection, location of warts on the body and other management practices.

The virus like particles of BPV–L1 capsid proteins are highly immunogenic, and develop potential humoral immune response in experimental animals (Liu et al., 2012; Jesus et al., 2012; Harnacker et al., 2017; Yang et al., 2021; Vrablikova et al., 2023). However, the development of VLPs is highly cost effective and required well established laboratories. Alternatively, the formaline inactivated autogenous vaccines are least cost effective, safe and easy to produced with minimal laboratory facilities. The practice of formalin inactivated autogenous vaccine was a traditional approach, and the hypothesis is that it provided the pathogen associated molecular patterns (PAMP) to the receptors of the host immune system. It was believed that the BPV-PAMPs are not only a good vaccine candidate but also a potent immune stimulatory component within the host (Amador-Molina et al., 2013). The BPV–PAMPs stimulates inflammatory cells, tumour necrosis factor-α, IL-1 and innate immune responses. These in turn stimulated the production of IL–6, which activated the cell mediated and humoral immune responses (Campo, 2006; Allen et al., 2015; Zhou et al., 2019). The activated immune system regulate the growth and progression of the BPV infection to malignancy form. During skin infections, the central circulating memory T –cells plays significant role in regulation of recurrence of infection (Jiang et al., 2012). Further, as part of supportive therapy, the chemotherapeutic drugs regulated the secondary bacterial infections and enhanced the early recovery of the animal. It was evident from our study that formalin inactivated autogenous vaccine in combination with chemotherapeutic drugs was proven effective in control of the BPV infections. So far, even after several months of treatment, no recurrence of the warts was noticed in the affected animals. The recurrence of infection was frequently noticed after surgical treatment of warts. Alternatively, formalin inactivated autogenous vaccine was reported as the best option under field conditions for control of BPV infections.

4. CONCLUSION

A combination of chemotherapy and formalin inactivated autogenous vaccine prepared from warts was the most preferred treatment for control of BPV infection. The BPV infected animals recovered rapidly and warts regressed with mild scars left behind. Our study provided insights in application of PAMPs of BPV as vaccine candidate for control of BPV infection.

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6. REFERENCES

Ablasser, A., Chen, Z.J., 2019. cGAS in action: Expanding roles in immunity and inflammation. Science. 363:eaat8657. doi: 10.1126/science.aat8657.

Allen, C.T., Clavijo, P.E., Van Waes, C., Chen, Z., 2015. Anti-tumour immunity in head and neck cancer: Understanding the evidence, how tumours escape and immunotherapeutic approaches. Cancers 7(4), 2397–2414.

Amador-Molina, A., Hernández-Valencia, J.F., Lamoyi, E., Contreras-Paredes, A., Lizano, M., 2013. Role of innate immunity against human papillomavirus (HPV) infections and effect of adjuvants in promoting specific immune response. Viruses 5(11), 2624–2642. doi: 10.3390/v5112624. PMID: 24169630; PMCID: PMC3856406.

Baker, C.C., Phelps, W.C., Lindgren, V., Braun, M.J., Gonda, M.A., Howley, P.M., 1987. Structural and

transcriptional analysis of human papillomavirus type 16 sequences in cervical carcinoma cell lines. Journal of Virology 61(4), 962–971.

Batista, M.V., Silva, M.A., Pontes, N.E., Reis, M.C., Corteggio, A., Castro, R.S., Borzacchiello, G., Balbino, V.Q., Freitas, A.C., 2013. Molecular epidemiology of bovine papillomatosis and the identification of a putative new virus type in Brazilian cattle. The Veterinary Journal 197(2), 368–373.

Bertagnolli, A.C., Bezerra, A.V.A., Santos, R.N., Cavalli, L.S., Varela, A.P.M., Reis, E.M., Cibulsky, S.P., Roehe, P.M., Mayer, F.Q., 2020. Clinicopathological characteristics and papillomavirus types in cutaneous warts in bovine. Brazilian Journal of Microbiology 51(1), 395–401. doi: 10.1007/s42770-019-00121-2. Epub 2019 Aug 7. PMID: 31388938; PMCID: PMC7059983.

Bocaneti, F., Altamura, G., Corteggio, A., Velescu, E., Roperto, F., Borzacchiello, G., 2016. Bovine Papillomavirus: new insights into an old disease. Transboundary and Emerging Diseases 63(1), 14–23. https://doi.org/10.1111/tbed.12222.

Borzacchiello, G., Roperto, F., 2008. Bovine papillomaviruses, papillomas and cancer in cattle. Veterinary Research 39(5), 1–13. https:// doi.org/10.1051/vetres:2008022.

Campo, M.S., 2006. Papillomavirus research: from natural history to vaccines and beyond. Caister Academic Press, Norfolk, UK. 424 pp.

Chen, Q., Sun, L., Chen, Z.J., 2016. Regulation and function of the cGAS-STING pathway of cytosolic DNA sensing. Nature Immunology 10, 1142–1149. doi: 10.1038/ni.3558.

De Falco, F., Cutarelli, A., Gentile, I., Cerino, P., Uleri, V., Catoi, A.F., Roperto, S., 2021. Bovine *Delta* Papillomavirus E5 oncoprotein interacts With TRIM25 and hampers antiviral innate immune response mediated by RIG-I-Like receptors. Frontiers in Immunology. Jun 10, 12, 658762. doi: 10.3389/ fimmu.2021.658762. PMID: 34177899; PMCID: PMC8223750.

Fang, R., Jiang, Q., Guan, Y., Gao, P., Zhang, R., Zhao, Z., 2021. Golgi apparatus synthesized sulfated glycosaminoglycans mediate polymerization and activation of the cGAMP sensor STING. Immunity. 54, 962–75.e8. doi: 10.1016/ J.immuni.2021.03.011.

Freitas, A.C., Silva, M.A.R., Jesus, A.L.S., Mariz, F.C., Cordeiro, M.N., Albuquerque, B.M.F., Batista, M.V.A., 2011. Recent insights into bovine papillomavirus. African Journal of Microbiology Research 5(33), 6004–6012. https://doi.org/10.5897/ AJMRX11.020.

Guey, B., Ablasser, A., 2022. Emerging dimensions of cellular cGAS-STING signaling. Current Opinion in Immunology 74, 164–171. doi: 10.1016/j. coi.2022.01.004.

Harnacker, J., Hainisch, E.K., Shafti-Keramat, S., Kirnbauer, R., Brandt, S., 2017. Type specific L1 virus-like particle-mediated protection of horses from experimental bovine papillomavirus 1-induced pseudo-sarcoid formation is long-lasting. Journal of General Virology 98(6), 1329–1333. doi: 10.1099/ jgv.0.000791.

Hauck, M.L., 2008. Papillomatosis (1st Edn.). In: five-minute veterinary consult: Ruminant. Wiley-Blackwell, Iowa, USA, 662–663.

Ishikawa, H., Barber, G.N., 2008. STING is an endoplasmic reticulum adaptor that facilitates innate immune signalling. Nature 455, 674–678. doi: 10.1038/ nature07317.

Jesus, A.L., Mariz, F.C., Souza, H.M., Cordeiro, M.N., Coimbra, E.C., Leitao, M.C., Nascimento, L.M., Stocco, R.C., Beçak, W., Freitas, A.C., 2012. Expression of the bovine papillomavirus type 1, 2 and 4 L1 genes in the yeast Pichia pastoris. Genetics and Molecular Research 11(3), 2598–2607. doi: https:// doi.org/10.4238/2012.july.19.2.

Jiang, X., Clark, R.A., Liu, L., Wagers, A.J., Fuhlbrigge, R.C., Kupper, T.S., 2012. Skin infection generates non-migratory memory CD8+T(RM) cells providing global skin immunity. Nature 483(7388), 227–231. doi: 10.1038/nature10851. PMID: 22388819; PMCID: PMC3437663.

Khalid, N., Kamaruzaman, I.N.A., Yahya, S.N.C., Azeez-Okene, I.A., Reduan, M.F.H., Shaharulnizim, N., 2021. Application of autogenous vaccine for the treatment of bovine cutaneous papillomatosis type 2 in malaysia. Journal of Animal Health and Production 9(1), 1–4.

Kumar, P., Nagarajan, N., Saikumar, G., Arya, R.S., Somvanshi, R., 2015. Detection of bovine papilloma viruses in wart-like lesions of upper gastrointestinal tract of cattle and buffaloes. Transboundary and Emerging Diseases 62(3), 264–271. doi: 10.1111/ tbed.12127. Epub 2013 Jul 24. PMID: 23890104.

Li, K., Liu, Y., Xu, Z., Zhang, Y., Luo, D., Gao, Y., Qian, Y., Bao, C., Liu, C., Zhang, Y., Qi, X., Cui, H., Wang, Y., Gao, L., Wang, X., 2019. Avian oncogenic herpesvirus antagonizes the cGAS-STING DNA-sensing pathway to mediate immune evasion. PLoS Pathogens 20;15(9), e1007999. doi: 10.1371/ journal.ppat.1007999. PMID: 31539404; PMCID: PMC6799934.

Liu, F., Ge, S., Li, L., Wu, X., Liu, Z., Wang, Z., 2012.

Virus-like particles: potential veterinary vaccine immunogens. Research in Veterinary Science 93(2), 553–559. doi: 10.1016/j.rvsc.2011.10.018.

Liu, X., Zhang, M., Ye, C., Ruan, K., Xu, A., Gao, F., Tong, G., Zheng, H., 2021. Inhibition of the DNA-Sensing pathway by pseudorabies virus UL24 protein via degradation of interferon regulatory factor 7. Veterinary Microbiology 255, 109023. doi: 10.1016/j.vetmic.2021.109023. PMID: 33677368.

Lo Cigno, I., Calati, F., Albertini, S., Gariglio, M., 2020. Subversion of host innate immunity by human papillomavirus oncoproteins. Pathogens 9, 292. doi: 10.3390/pathogens9040292.

Luo, X., Donnelly, C.R., Gong, W., Heath, B.R., Hao, Y., Donnelly, L.A., Moghbeli, T., Tan, Y.S., Lin, X., Bellile, E., Kansy, B.A., Carey, T.E., Brenner, J.C., Cheng, L., Polverini, P.J., Morgan, M.A., Wen, H., Prince, M.E., Ferris, R.L., Xie, Y., Young, S., Wolf, G.T., Chen, Q., Lei, Y.L., 2020. HPV16 drives cancer immune escape via NLRX1-mediated degradation of STING. Journal of Clinical Investigation 1 130(4), 1635–1652. doi: 10.1172/JCI129497. PMID: 31874109; PMCID: PMC7108911.

Mayil kumar, K., Kokila, S., Manimuthu, P., Kuppusamy, G., 2014. Formalin inactivated autogenous vaccine for treatment of papillomatosis in adult dairy cow. The Indian Veterinary Journal. 91(10), 13–15.

Módolo, D.G., Araldi, R.P., Mazzuchelli-de-Souza, J., Pereira, A., Pimenta, D.C., Zanphorlin, L.M., Beçak, W., Menossi, M., de Cassia, Stocco, R., de Carvalho, R.F., 2017. Integrated analysis of recombinant BPV-1 L1 protein for the production of a bovine papillomavirus VLP vaccine. Vaccine 35(12), 1590–1593. doi: 10.1016/j.vaccine.2017.02.007.

Oliveira, M., Rodrigues, D.R., Guillory, V., Kut, E., Giotis, E.S., Skinner, M.A., Guabiraba, R., Bryant, C.E., Ferguson, B.J., 2021. Chicken cGAS Senses Fowlpox Virus Infection and Regulates Macrophage Effector Functions. Frontiers in Immunology. Feb 1;11:613079. doi: 10.3389/fimmu.2020.613079. PMID: 33633733; PMCID: PMC7901977.

Pathania, S., Dhama, K., Saikumar, G., Shahi, S., Somvanshi, R., 2012. Detection and quantification of bovine papilloma virus type 2 (BPV-2) by real-time PCR in urine and urinary bladder lesions in enzootic bovine haematuria (EBH)-affected cows. Transboundary and Emerging Diseases 59(1), 79–84. doi: 10.1111/j.1865-1682.2011.01248.x. Epub 2011 Jul 28. PMID: 21797988.

Salib, F.A., Farghali, H.A., 2011. Clinical, epidemiological and therapeutic studies on Bovine Papillomatosis in Northern Oases, Egypt in 2008. Veterinary World 4(2), 53–59. doi: 10.5455/vetworld.2011.53-59.

Stanley, M., 2006. Immune responses to human papillomavirus Vaccine 24(S1) 16–22. doi: 10.1016/j.vaccine.2005.09.002. PMID: 16219398.

Van Doorslaer, K., Tan, Q., Xirasagar, S., Bandaru, S., Gopalan, V., Mohamoud, Y., Huyen, Y., Mcbride, A.A., 2013. The papillomavirus episteme: a central resource for papillomavirus sequence data and analysis. Nucleic Acids Research 41(Database issue), D571–578. doi: 10.1093/nar/gks984.

Vrablikova, A., Brezani, V., Psikal, I., Fraiberk, M., Sebela, M., Fojtikova, M., Kulich, P., Hezova, R., Masek, J., 2023. Development of modern immunization agent against bovine papillomavirus type 1 infection based on BPV1 L1 recombinant protein. Frontiers in Veterinary Science. 10, 1116661. doi: 10.3389/fvets.2023.1116661.

Yang, D., Chen, L., Duan, J., Yu, Y., Zhou, J., Lu, H., 2021. Investigation of Kluyveromyces marxianus as a novel host for large-scale production of porcine parvovirus virus-like particles. Microb Cell Fact 20, 24. doi: 10.1186/s12934-021-01514-5.

Zhou, C., Tuong, Z.K., Frazer, I.H., 2019. Papillomavirus immune evasion strategies target the infected cell and the local immune system. Frontiers in Oncology 9, 682. doi: 10.3389/fonc.2019.00682.