

# Bovine Papillomatosis Shows a Persistent, Non-Regressive Course with High-Rate Coinfection in a Long-Term Study of a Dairy Herd

**Patrícia Gallindo Carrazzoni**

Universidade Federal Rural de Pernambuco

**Morse Edson Pessoa-Junior**

Universidade Federal de Pernambuco

**Fernando Tenório-Filho**

Instituto Agronômico de Pernambuco

**Ryan Vieira Alves**

Instituto Federal de Educação Ciência e Tecnologia da Paraíba

**Antonio Carlos de Freitas**

Universidade Federal de Pernambuco

**Maria Cristina de Oliveira Cardoso Coelho**

Universidade Federal Rural de Pernambuco

**Maria Silva**

`maria.ramos@ifpb.edu.br`

Federal Institute of Education, Science and Technology of Paraíba <https://orcid.org/0000-0002-7363-988X>

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## Research Article

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# Abstract

Bovine cutaneous papillomatosis, caused by Bovine papillomavirus (BPV), affects cattle worldwide; however, its clinical course and epidemiology remain incompletely understood. This study aimed to describe the clinical presentation, characteristics, and evolution of papillomas over a 24-month period, as well as to investigate the influence of different BPV types and viral coinfection. A long-term observational study was conducted with 42 Girolando 5/8 cattle, aged between one and 16 years, from a bracken fern-free experimental station in northeastern Brazil. Lesions were evaluated according to type, color, appearance, size, and anatomical location. Samples from 35 papillomas collected from 16 animals were subjected to molecular identification of BPV and coinfection analysis by PCR using primers specific for BPV types 2–6 and 8–12. The results demonstrated a predominance of mild cutaneous papillomatosis, characterized by atypical basal, multiple BPV-type papillomas, with no progression to severe forms or complete regression during the follow-up period. Co-infection was observed in all papillomas, ranging between five and nine different virus types per papilloma. BPV types 2 and 3 were the most frequently detected. No association was observed between papilloma type, location, or severity and BPV type or coinfection status. In conclusion, mild cutaneous papillomatosis showed a persistent pattern in the studied herd, with a high frequency of BPV-2 and BPV-3 and frequent coinfections, which should be considered in disease management strategies and in the development or application of vaccination protocols.

## Introduction

Bovine cutaneous papillomatosis is an infectious disease caused by Bovine papillomavirus (BPV), which affects the basal cells of the epithelium and subepithelial fibroblasts, resulting in benign tumor-like lesions on the skin and mucosa, known as papillomas or warts [1]. BPV infection is influenced by various factors, including the genetics of the animals, their environment and their diet [3, 4, 5, 6]. BPVs are known to cause different types of papillomas, varying in appearance and severity. BPV belongs to the Papillomaviridae family, which is characterized by a large genetic and phenotypic diversity [7].

Previous studies on the molecular epidemiology of BPVs have correlated the identification of viral types with tropism for specific locations and lesions [8, 9]. Various research indicates the simultaneous presence of multiple BPV types in the same lesion, characterizing co-infections [7, 8, 10, 14].

Lesions induced by BPV present as typical papillomas, atypical basal papillomas, atypical embedded papillomas, and filiform papillomas [2, 15, 16]. They appear white, grayish, or pink, with a dry and keratinized surface, varying in size from 1 mm to 500 mm [2]. They are more common on the head, neck, dewlap, limbs, udder, and penis, areas subjected to friction and minor bruises. According to the literature, it mainly affects young animals, and its development is associated with factors such as immunosuppression, poor nutrition, parasitosis, stress, improper management, and the use of immunosuppressive drugs [17, 18]. Some lesions may persist in animals exposed to stressful factors and can develop into malignant tumors under the influence of environmental co-factors [18].

The presence of papillomatous lesions leads to economic losses that are often not recognized by producers as a consequence of cutaneous papillomatosis. This negligence exacerbates infection within the herd and favors disease spread. Ongoing studies are needed for a better understanding of infection, pathogenesis, clinical disease, and virus biology [19]. The importance of these results lies in contributing to the treatment, prevention, and control of the disease and in discussing vaccination strategies that cover a broad spectrum, considering that BPV-induced immunity is type-specific [20, 21].

This study aimed to describe the clinical evolution of bovine cutaneous papillomatosis over 24 months and characterize the associated BPV types and coinfection rates. Specifically, it evaluated a bovine herd affected by papillomatosis with respect to lesion characteristics, BPV infection status, viral type frequency, and the clinical evolution of the lesions over time.

## **Materials and Methods**

### **Ethical Aspects**

This study was approved by the Animal Ethics Committee (CEUA) of the Universidade Federal Rural de Pernambuco – UFRPE (protocol number N°23082.013040/2015-49).

### **Animals**

The study was conducted at the Pernambuco Agronomic Institute (IPA) - Itambé, Experimental Station (EEI), located in the microregion of the Northern Forest Zone in Pernambuco State, and at the Laboratory of Molecular Studies and Experimental Therapy (LEMTE) of the Department of Genetics of the Universidade Federal de Pernambuco (UFPE).

Forty-two dairy cows showing cutaneous papillomas, aged between one and sixteen years of the Girolando 5/8 breed, from IPA - EEI, were selected. They were identified by numbered ear tags. The animals, raised semi-intensively, consumed *Brachiaria* pastures in clean paddocks free of bracken fern (*Pteridium aquilinum*), and received supplemental feeding during drought periods with elephant grass (*Pennisetum purpureum*) and sugarcane (*Saccharum* spp), as well as water and mineral salt specific for cattle *ad libitum*. The herd was dewormed and vaccinated against rabies, foot-and-mouth disease, and brucellosis. Reproductive management used exclusive artificial insemination, with no bulls present, and milking was done manually, in the morning and afternoon shifts.

### **Papillomas Analysis**

Papillomas were analyzed based on macroscopic parameters such as type, color, appearance, size, and location. The number of lesions was determined by their distribution on the animal's body and classified as mild (up to 25% of the body affected), moderate (between 25% and 50% of the body affected), and severe (more than 50% of the body affected). Papillomas were evaluated through observation and

photographic images, cataloged in individual monitoring records, following the methodology described by Munday (2017) [2].

To evaluate BPV infection in papillomas, 35 fragments of typical, atypical, and filiform papillomas were randomly collected from 16 young animals (which are commonly affected in nature due to their still-developing immune system) from different body regions, such as the head, back, limbs, udder, tail, neck, dewlap, and abdomen, by detachment or, when necessary, by biopsy of regions previously anesthetized with 2% lidocaine and elliptical incision with a scalpel blade. The samples were stored in refrigerated containers and sent to LEMTE. For each animal, papillomas with different types/characteristics were collected. All samples were collected on the same day.

## **DNA Extraction**

Genomic DNA was extracted from 20 mg fragments of papillomas using the Wizard Genomic Purification A1125® PROMEGA Kit, following the manufacturer's instructions. The extracted DNA was quantified using the Nanovue® GE and quality was assessed by Polymerase Chain Reaction (PCR) of the  $\beta$ -globin gene according to the conditions described in another study [11].

## **BPV Detection**

For the diagnosis of BPV infection and virus genotyping, viral DNA was amplified using PCR with Promega Master Mix Kit® and BPV type-specific primers (BPV2-6 and BPV8-12) according to the conditions described in another study [28]. All amplified products were visualized by electrophoresis on a 2% agarose gel with TAE buffer, stained with ethidium bromide, and photographed.

Animals were evaluated for BPV infection status, frequency of viral types in papillomas, presence of co-infection, and the relationship between viral types and papillomas characteristics. The clinical evolution of the papillomas was monitored for a period of 24 months.

## **Statistical Analysis**

The number of BPV types detected per papilloma was compared between typical and atypical lesions using the Mann-Whitney U test, and among anatomical locations using the Kruskal-Wallis test. The association between anatomical location and papilloma type was assessed using Fisher's exact test. A p-value < 0.05 was considered statistically significant.

## **Results**

The study results indicated that mild cutaneous papillomatosis occurred in 26 of the 42 animals (62%), moderate papillomatosis in 13 of the 42 animals (31%), and severe papillomatosis in 3 of the 42 animals (7%). It was observed that young animals, aged between one and three years, were the most affected,

representing 74% (31 of 42) of the affected animals. Among these young animals, 61% (19 of 31) had mild lesions, 32% (10 of 31) had moderate lesions, and 6.5% (2 of 31) had severe lesions (Fig. 1). The size of the papillomas ranged from 0.5 to 8 cm, and the lesions presented as single types or in combinations of various types, sometimes complicating specific identification.

Macroscopic analysis of the papillomas revealed that the atypical basal type, characterized by a rough appearance and infection on the back, was the most frequent. In mild cases of papillomatosis, pedunculated, filiform, or mixed papillomas were not observed. Atypical papillomas appeared as single, small lesions (up to 1 cm) scattered across various parts of the animals' bodies. In moderate and severe forms, the most frequent types were typical pedunculated papillomas, multiple atypical basal papillomas, and mixed papillomas. The color of the papillomas varied between yellowish-white, pink, gray, and black.

Papillomas on the limbs were the most frequent, followed by lesions located on the udder/teats, withers/back, dewlap, and head, which presented similar frequencies. Other less common locations included the linea alba, the umbilical fold, the tail, and scar areas (Fig. 2).

For clinical follow-up, all papillomas of each animal were previously identified and recorded in anatomical diagrams according to their location. In subsequent evaluations, the animals were monitored for lesion regression, increase in size, or the appearance of new papillomas. No involution or increase in lesion size was observed throughout the evaluated period; however, a few new papillomas appeared, mainly in areas subject to trauma.

In the quantitative analysis, each papilloma was counted as a unit, regardless of its extent, with continuous lesions considered as a single occurrence until interruptions were present. From this count, a papilloma occurrence score was established by anatomical location.

Out of the 35 papillomas collected, all were infected with Bovine papillomavirus. The most frequent viral types were BPV2 and BPV3, present in 100% of the papillomas (35 out of 35), while BPV9 was the least frequent, occurring in 31% of the papillomas (11 out of 35). BPV2, BPV3, and BPV11 were also highly prevalent (each detected in at least 89% of papillomas), while BPV9 was comparatively rare (Fig. 3). These associations were formally tested: the number of BPV types per papilloma did not differ significantly between typical and atypical lesions (Mann-Whitney  $U = 130$ ,  $p = 0.305$ ) or among anatomical locations (Kruskal-Wallis  $H = 2.20$ ,  $p = 0.531$ ). However, anatomical location was significantly associated with papilloma type (Fisher's exact test,  $p < 0.0001$ ) (Table 1).

Table 1

Association between clinical features and viral coinfection parameters in bovine cutaneous papillomas.

| Variable 1                                                                                                                   | Variable 2          | Groups compared                                                    | Statistical test    | Test statistic | p-value  | Significance |
|------------------------------------------------------------------------------------------------------------------------------|---------------------|--------------------------------------------------------------------|---------------------|----------------|----------|--------------|
| Number of BPV types                                                                                                          | Type of lesion      | Typical (n = 20) vs. Atypical (n = 15)                             | Mann-Whitney U      | U = 130        | 0.305    | ns           |
| Number of BPV types                                                                                                          | Anatomical location | Head/neck (n = 9), Dorsum (n = 11), Ventral (n = 6), Other (n = 9) | Kruskal-Wallis      | H = 2.20       | 0.531    | ns           |
| Anatomical location                                                                                                          | Type of lesion      | Head/neck, Dorsum, Ventral, Other vs. Typical/Atypical             | Fisher's exact test | —              | < 0.0001 | ***          |
| <i>Abbreviations: ns = not significant (<math>p &gt; 0.05</math>); *** = highly significant (<math>p &lt; 0.001</math>).</i> |                     |                                                                    |                     |                |          |              |

Co-infection was observed in all papillomas, ranging between five and nine different virus types per papilloma. The association of Delta and Xi-PV genera occurred in 31% of the papillomas (11 out of 35), and the association of Delta, Epsilon, and Xi-PV genera occurred in 68.5% of the papillomas (24 out of 35).

During the 24-month follow-up, no animal showed complete regression of the papillomas. Only one young animal (1 out of 42, 2%) showed spontaneous improvement, with a reduction from severe to moderate papillomas after 24 months. Three animals (3 out of 42, 7%) died; they were young, between one and two years old, and had severe (one animal) and moderate (two animals) papillomas.

## Discussion

Based on the results obtained, it was possible to identify two distinct clinical presentations in the herd. The first, present in most animals (62%), was mild, with few, small, single papillomas with no specific area preference, often unnoticed. The second clinical presentation was more severe and evident, occurring in 38% of the animals, and showed all the clinical characteristics reported in cutaneous papillomatosis [15, 1, 18].

Contrary to the classical description of bovine cutaneous papillomatosis as a self-limiting disease in immunocompetent hosts [1, 18], our 24-month follow-up revealed an absence of complete regression in any animal, regardless of age or initial lesion severity. Only one young animal showed partial improvement. This unexpected persistence challenges the current understanding of the natural history of BPV infection. While Campo (1994) and Borzacchiello (2008) [6, 18] associate regression with the absence of environmental co-factors, our study was conducted in a bracken fern-free environment with good management practices, suggesting that other factors, such as viral diversity or host genetics, may be more critical determinants of lesion outcome than previously acknowledged.

The clinical heterogeneity observed within this uniformly managed cohort—ranging from mild, unnoticed lesions to severe, widespread papillomatosis—strongly implicates host-related factors in disease outcome. Although all animals were raised under identical conditions (nutrition, hygiene, absence of bracken fern), the variability in lesion severity points towards intrinsic differences in susceptibility. Longeri et al. (2021) [23] provided evidence for this by associating BoLA-DRB3 polymorphisms (MHC class II) with the risk of BPV-associated bladder tumors. While our previous investigation into MBL2 polymorphisms (a key innate immune gene) did not reveal an association with papillomatosis susceptibility in this herd [24], the role of other immune-related genes, particularly those within the MHC complex, warrants further investigation. It is plausible that the ability to mount an effective type-specific immune response against a backdrop of high coinfection is genetically constrained in some animals, leading to the persistent, severe phenotype.

The atypical basal papilloma type did not occur in the presence of moderate and severe symptoms, which may suggest a relationship between papilloma type and lesion severity; however, this pattern was not formally tested statistically and should be interpreted with caution given that no association was reported elsewhere in the study. Lesions on scars suggest that papillomas appeared in areas with mechanical lesions such as cuts and scratches.

Notably, statistical analysis revealed a significant association between anatomical location and papilloma type (Fisher's exact test,  $p < 0.0001$ ), indicating that the distribution of lesion types is not random across body regions. This finding, together with the observation that atypical basal papillomas did not co-occur with moderate or severe presentations, suggests that local tissue or microenvironmental factors at specific anatomical sites may influence which papilloma morphology develops, independently of BPV type or coinfection status.

The detection of coinfection with five to nine different BPV types in every single papilloma analyzed (100%) aligns with the growing body of evidence highlighting the genetic complexity of BPV infections in cattle worldwide [8, 11, 13, 29]. However, the universality of coinfection in this herd, combined with the persistent clinical course, allows us to propose a mechanistic hypothesis. We speculate that the constant and simultaneous presence of multiple BPV types (Delta, Epsilon, and Xi-PV genera) may overwhelm or dysregulate the host's immune system. This phenomenon, analogous to that observed in persistent high-risk HPV infections in humans, could involve immune interference between viral types or the suppression of type-specific cytotoxic T-lymphocyte responses, leading to chronic lesion maintenance rather than clearance [20]. The findings of this study have direct implications for the design of vaccination strategies. Since BPV-induced immunity is type-specific [20, 21], the high frequency of coinfection and the presence of up to nine different types in a single lesion suggest that a monovalent vaccine would be largely ineffective in this herd. Any successful prophylactic approach would likely require a multivalent formulation, covering at least the most prevalent types (BPV-2 and BPV-3, found in 100% of lesions) but ideally also including less frequent types to prevent their potential expansion post-vaccination. This challenge is compounded by evidence of vertical transmission [28, 33] and the presence of BPV in asymptomatic animals [30], indicating that the virus is deeply entrenched in the herd.

However, this study has limitations that must be considered when interpreting these results. First, the molecular analysis was performed on a subset of 16 animals and 35 lesions. While representative, a larger sample size could reveal additional viral types or associations. Second, our PCR panel was restricted to BPV types 2–6 and 8–12. The absence of testing for BPV-1, -7, and more recently described types (> 12) means we may have underestimated the true viral diversity. Finally, the absence of bracken fern, while a strength for controlling a major co-factor, also means these results may not be generalizable to herds in environments where such co-factors are present.

Previous studies define cutaneous papillomatosis as self-limiting, with total regression of lesions in the absence of environmental co-factors. However, in this study, no regression or remission of lesions was observed in any of the animals, suggesting changes in disease pathogenesis. The low mortality found is consistent with the literature, which attributes death to cases with a high number of papillomas in critical areas such as the mouth, esophagus, and upper respiratory tract, or in the presence of environmental co-factors that lead lesions to malignancy [18].

## **Conclusion**

The results indicate that bovine cutaneous papillomatosis presents clinical variability, with most animals exhibiting mild, non-progressive lesions. Complete lesion regression was not observed, suggesting persistent BPV-associated infection. Management factors such as colostrum intake, hygiene, and nutrition during development may plausibly contribute to milder clinical presentations; however, these variables were not directly assessed in the present study and remain hypotheses to be tested in dedicated investigations. The frequent co-infection with multiple BPV types underscores the presence of viral diversity within the herd. Overall, these findings provide descriptive data on the clinical profile of bovine cutaneous papillomatosis and may support future studies on management and control strategies. The persistent nature of lesions and high frequency of coinfection with multiple BPV types challenge the notion of papillomatosis as a self-limiting disease and have significant implications for the development of effective, broad-spectrum vaccines.

## **Declarations**

### **Ethical approval**

All of the reported work is original and prevailing local, national and international regulations and conventions, and normal scientific ethical practices, have been respected. This study was approved by the Animal Ethics Committee (CEUA) of the Universidade Federal Rural de Pernambuco – UFRPE (protocol number N°23082.013040/2015-49).

### **Consent to participate / Consent for publication**

Not applicable.

# Competing interests

The authors declare no conflict of interest.

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# Author contributions

P.G.C. conceptualized the investigation, conducted the molecular experiments and analysed the animals; M.E.P.J conducted the molecular experiments; F.T.F analysed the animals; R.V.A. drafted the manuscript; A.C.F. supervised the molecular experiment; M.C.O.C.C. conceptualized and supervised the investigation and M.A.R.S conducted the molecular experiments and drafted the manuscript.

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Not stated in the original manuscript.

# Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. [Author note: this statement was not present in the original manuscript and is inserted here as a placeholder in line with Research Square's requirements — please confirm or replace it with the wording that reflects where your data actually reside, e.g., a repository link, before submission.]

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## Figures

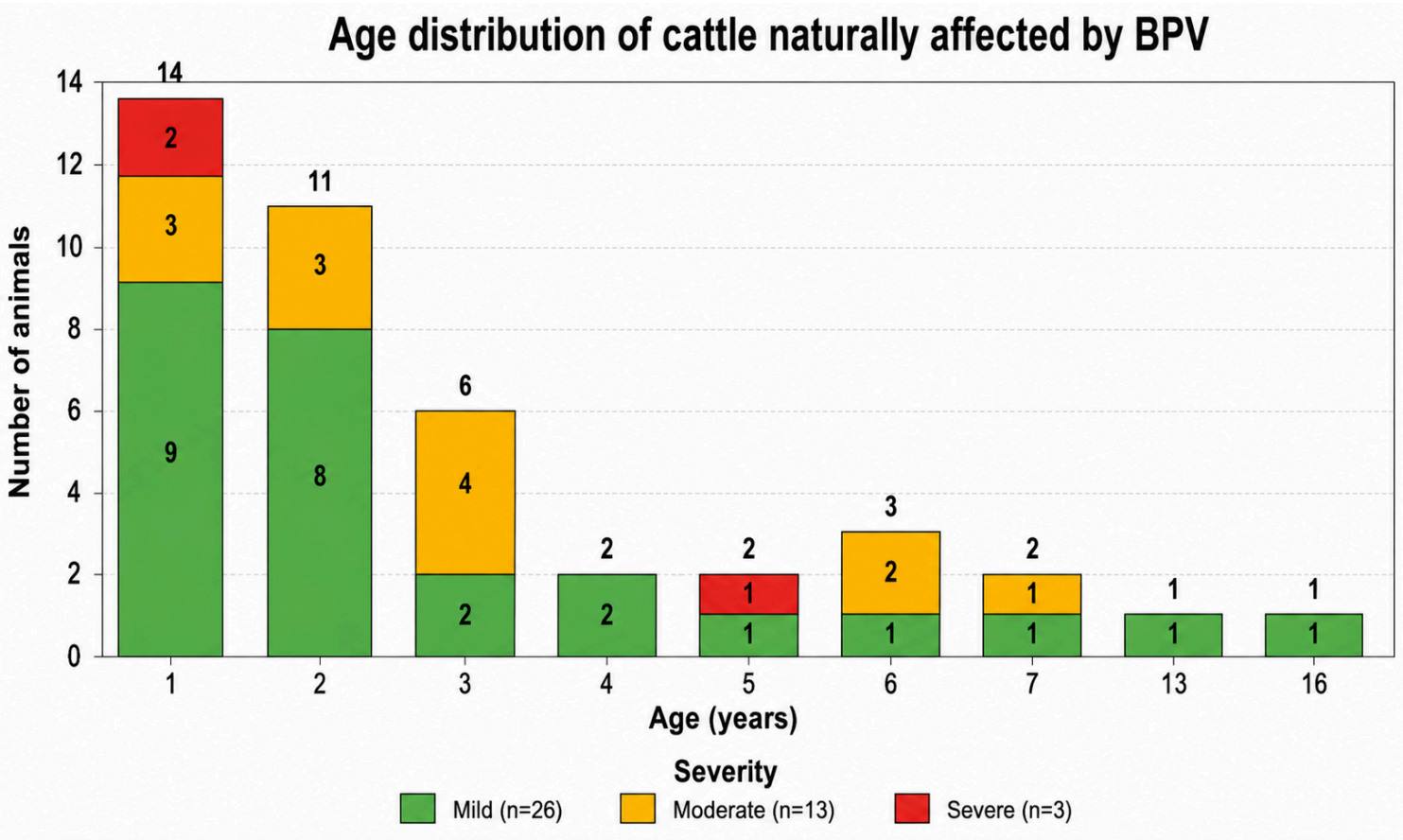


Figure 1

Age distribution of 42 dairy cows naturally affected by bovine cutaneous papillomatosis, categorized by lesion severity (mild, moderate, severe). Each number on the x-axis (1 to 16) represents the age of the animals in years. Bars indicate the total number of animals at each age, with colors representing the severity of papillomatosis.

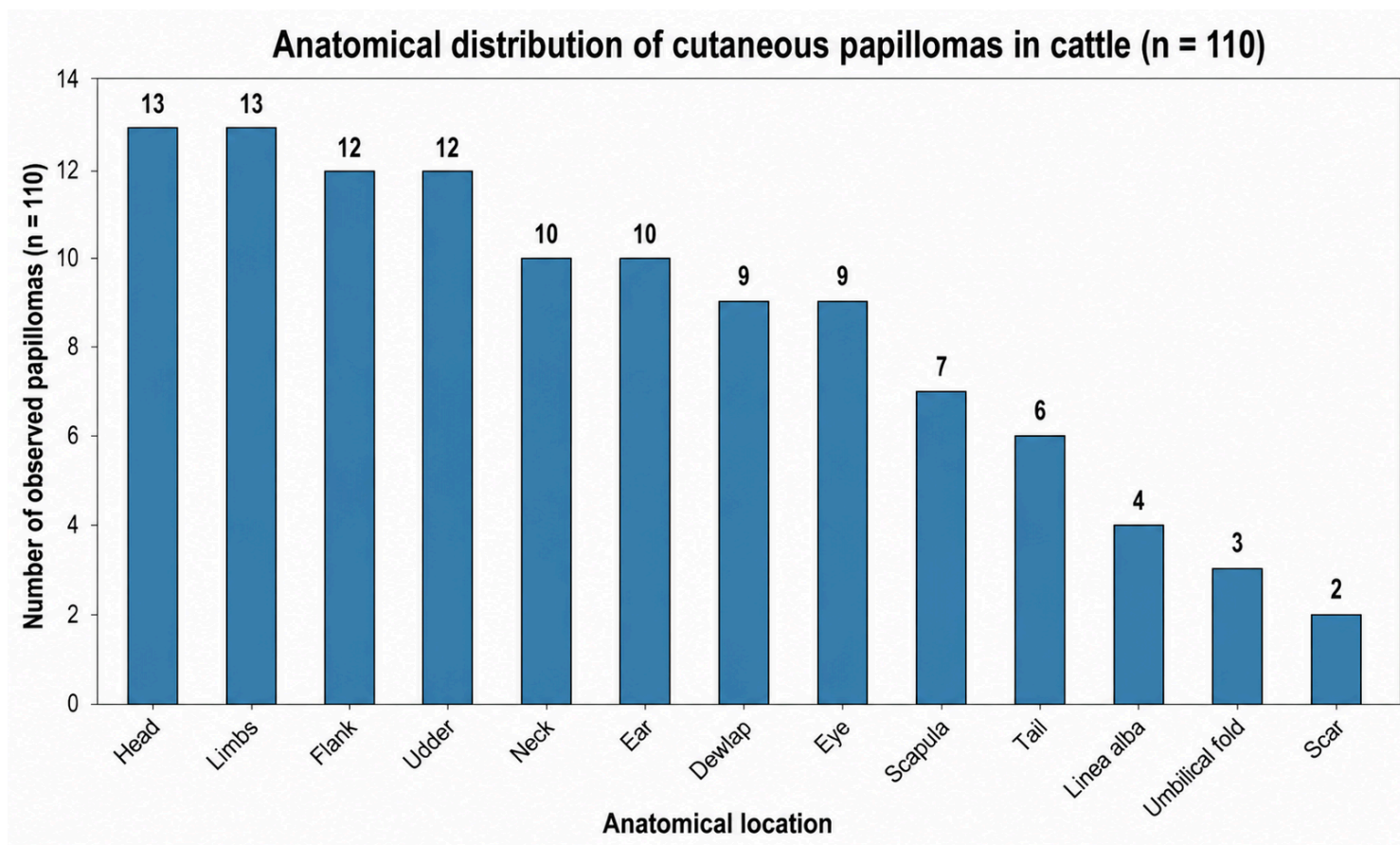


**Figure 2**

Anatomical distribution of cutaneous papillomas observed in cattle. A total of 110 papillomas were recorded across 13 anatomical locations.

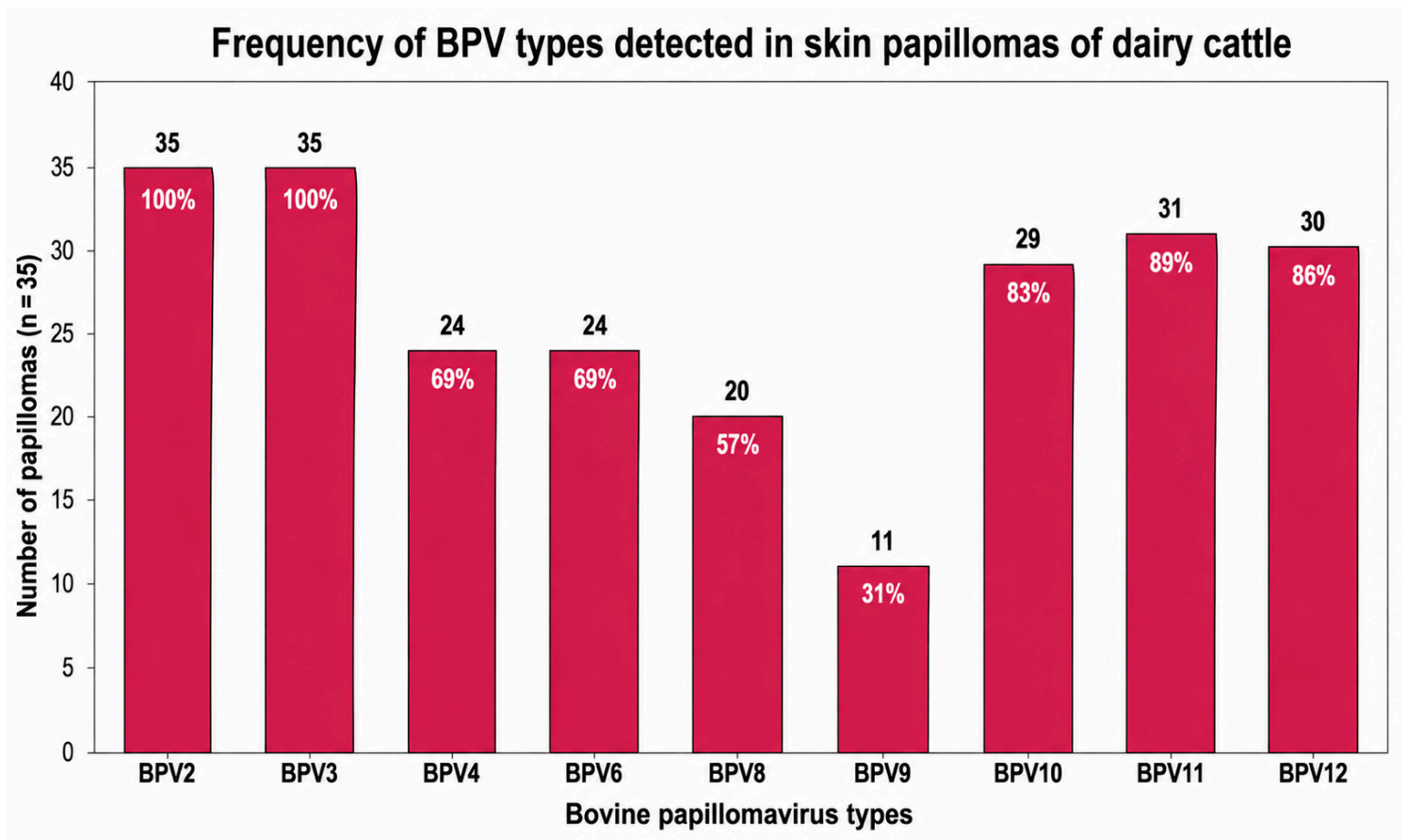


**Figure 3**

Frequency of BPV types detected in 35 skin papillomas collected from dairy cattle naturally infected with bovine papillomavirus.