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RESEARCH ARTICLE



Descriptive analysis of pediatric laryngeal papillomatosis in Republic of Moldova: epidemiological and clinical characteristics

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ABSTRACT

Introduction. Recurrent laryngeal papillomatosis is a rare but significant pediatric condition caused by human papillomavirus types 6 and 11. Characterized by the repeated growth of benign exophytic lesions in the respiratory tract, recurrent laryngeal papillomatosis poses a considerable burden due to its recurrent nature, frequent need for surgical intervention, and potential impact on respiratory function. This study aims to describe the epidemiological profile of pediatric recurrent laryngeal papillomatosis in the Republic of Moldova, identify high-risk groups, and explore the socioeconomic implications of the disease.

Material and methods. A retrospective, descriptive observational study was conducted using national data from 198 pediatric patients diagnosed with recurrent laryngeal papillomatosis and treated at the *Emilian Coțaga* Pediatric Otorhinolaryngology Clinic between 1981 and 2013. Demographic, clinical, and epidemiological variables were analyzed, including age at onset, sex, incidence, prevalence, and geographic distribution. Statistical analysis included descriptive methods, correlation coefficients, and linear regression models. Data were processed using Microsoft Excel and Python, with significance set at $p < 0.05$, for the 95% confidence interval.

Results. The average annual incidence was approximately 6 new cases, with a peak of 15 in certain years. The estimated prevalence reached 4.2 per 100 thousand children. Most patients were male, and the disease commonly manifested at ages 1 and 4. Correlation analysis revealed strong associations between age, sex, and disease onset, particularly in males. Linear regression confirmed the predictive value of demographic variables, though the model's robustness is limited by sample size. No progression into adulthood was observed, and seasonal or cyclical patterns were not evident.

Conclusions. Pediatric recurrent laryngeal papillomatosis in the Republic of Moldova shows a male predominance and early age of onset, with a consistent but relatively low incidence rate. Demographic indicators may aid in identifying at-risk populations, while early diagnosis and multidisciplinary management are essential to prevent complications. Expanding human papillomavirus vaccination coverage remains a critical public health priority. The findings support the need for prospective, multicenter research integrating vaccination status and immunological biomarkers to enhance disease prevention and control strategies.

Keywords: recurrent laryngeal papillomatosis, epidemiology, children.

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Key messages

What is not yet known about the issue addressed in the submitted manuscript

Recurrent respiratory papillomatosis in children has been studied internationally, but data on its epidemiology, incidence, and demographics in the Republic of Moldova are scarce. The roles of gender, age at onset, and regional differences in case detection and referral remain poorly understood. This study aims to fill these gaps by offering a detailed epidemiological analysis focused on the Moldovan pediatric population and identifying factors that may influence disease presentation.

The research hypothesis

Within the pediatric population of the Republic of Moldova, epidemiological factors and referral patterns significantly influence the incidence and clinical presentation of laryngeal papillomatosis.

The novelty added by manuscript to the already published scientific literature

This manuscript provides the first comprehensive epidemiological analysis of pediatric laryngeal papillomatosis specific to the Republic of Moldova. It identifies unique demographic patterns and potential regional factors influencing disease onset and clinical presentation within this population. Additionally, it highlights gaps in local healthcare management and offers data that can guide targeted interventions and future research.

Introduction

Recurrent laryngeal papillomatosis is a benign condition affecting the mucosa of the respiratory tract, characterized by the repeated formation of exophytic lesions caused by infection with the human papillomavirus. Although often referred to as glottic or laryngeal papillomatosis, the disease can affect any part of the respiratory tract [1-3]. Despite being relatively rare, recurrent laryngeal papillomatosis's tendency to recur and its impact on respiratory function pose a significant challenge for both patients and healthcare systems [4-6]. Males are more frequently affected than females [6, 7]. Clinical manifestations may resemble other common respiratory conditions, such as asthma or bronchitis, which can delay diagnosis and the initiation of appropriate treatment [7, 8]. In severe cases, airway obstruction may require urgent interventions, including tracheotomy, to ensure adequate breathing [9, 10].

The incidence of recurrent laryngeal papillomatosis varies significantly worldwide, influenced by factors such as human papillomavirus infection rates, access to medical care, and case reporting practices. In the pediatric population, the estimated incidence ranges from 0.2 to 2.1 cases per 100 thousand children annually, with reported prevalence between 0.8-4.3 per 100,000. The juvenile form is characterized by the recurrent appearance of exophytic lesions in the larynx, and disease severity can vary widely, often requiring frequent surgical interventions and adjuvant therapies [10-13].

A clear understanding of the epidemiological aspects of recurrent laryngeal papillomatosis is essential for developing effective strategies for the prevention, early detection, and management of this rare but impactful condition affecting children's health. In this context, the present chapter analyzes the demographic distribution of recurrent laryngeal papillomatosis in the Republic of Moldova, based on data collected over recent decades, highlighting trends in incidence and prevalence by age, sex, and time period. Special attention is given to identifying high-risk groups and the local particularities of disease progression [14, 15].

At the same time, the study evaluates the social and economic implications of the disease, taking into account the costs associated with repeated hospitalizations, surgical treatments, and the psychological impact on affected children and their families. The analysis is based exclusively on national statistical data, providing an updated and context-specific overview for the Republic of Moldova. This in-

formation may support the development of public health policies, the adjustment of human papillomavirus vaccination strategies, and the improvement of clinical management. By identifying region-specific needs, the study aims to support informed decision-making in the field of pediatric otorhinolaryngology.

Given the lack of consolidated epidemiological data on recurrent laryngeal papillomatosis in the pediatric population of the Republic of Moldova, this study aims to make a significant contribution to understanding the national distribution and progression of the disease. The statistical analysis of cases recorded over an extended period provides a solid foundation for evaluating the impact of this condition on both the healthcare system and patients. The findings may serve as a starting point for developing tailored preventive measures, optimizing therapeutic intervention strategies, and supporting vaccination and medical education initiatives among the general population and healthcare professionals.

Material and methods

The study was designed as an observational, descriptive, cross-sectional study during the years 1981-2013, aiming to assess the clinical-epidemiological characteristics and morbidity associated with recurrent laryngeal papillomatosis in the pediatric population of the Republic of Moldova. Ethical approval for the research was granted by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy, under decision no. 9, dated September 20, 2019.

The study analyzed data from 198 patients diagnosed with recurrent laryngeal papillomatosis who were admitted to the *Emilian Coțaga* Pediatric Otorhinolaryngology Clinic during the period 1981-2013.

The study included children up to 18 years old with a confirmed diagnosis of recurrent laryngeal papillomatosis. The diagnosis was established based on clinical and histopathological criteria. Patients with incomplete data or unconfirmed diagnoses were excluded.

The evaluation included demographic data (age, sex, and residence), medical and social factors, clinical details (age at disease onset, lesion sites), and epidemiological metrics (incidence and prevalence). The progression of the disease was followed for each patient over a period varying between 1 and 15 years.

The study was organized into clearly defined stages: setting objectives, selecting the sample, collecting data through

medical records and questionnaires, processing and statistically analyzing the information, synthesizing the results, and formulating conclusions with practical applicability. Comparative analyses of demographic, geographic, and temporal data were performed to reveal key trends and disparities.

Data processing was performed using Microsoft Excel and Python (Jupyter Notebook) software. Both descriptive and inferential statistical methods were applied. Quantitative indicators were expressed using the arithmetic mean (M), median (Me), and mode (Mo).

The Shapiro-Wilk test was applied to assess the normality of the data distribution. Relationships between variables were examined using linear regression, a model that allows the evaluation of dependence between a scalar response and multiple independent variables.

Values of $p < 0.05$ were considered statistically significant, with results reported alongside 95% confidence intervals.

The results were organized into tables, graphs (histograms), and charts (including structural, column, and bar charts). Typological and variation analyses were performed based on the grouping of key indicators.

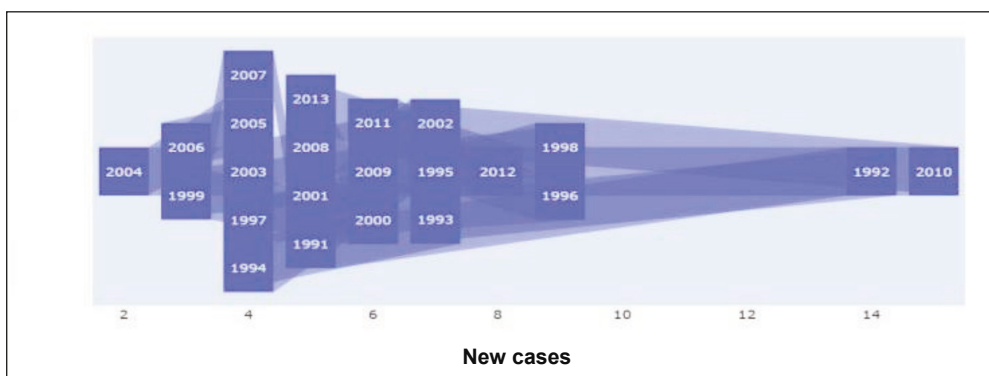


Fig. 1 Frequency of new cases between 1991-2013

Note: Each block represents a calendar year, plotted against the number of newly diagnosed cases. The absence of pronounced fluctuations supports the hypothesis of a stable incidence over time, with no apparent cyclical or seasonal patterns.

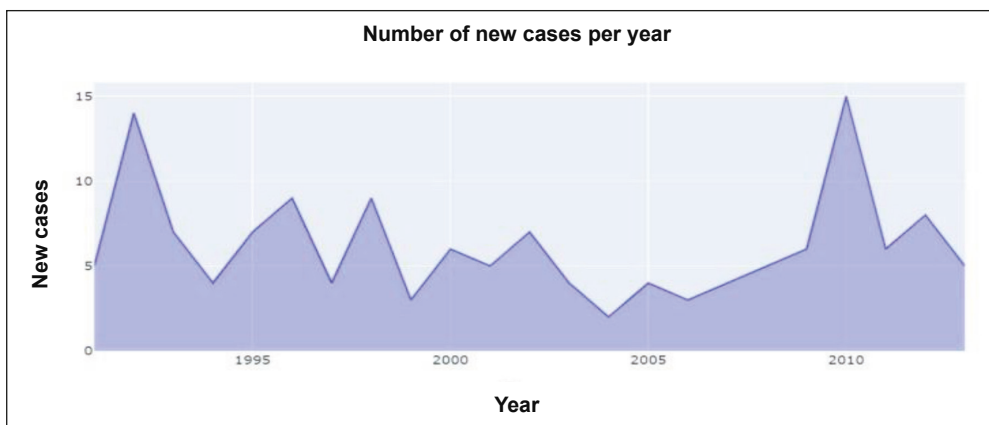


Fig. 2 The distribution of cases per year.

Note: The graph shows the temporal distribution of new cases over the analyzed period, highlighting interannual variations without a consistent upward or downward trend. Isolated fluctuations may be attributed to reporting factors, access to care, or local epidemiological particularities.

A retrospective analysis of cases of laryngeal papillomatosis in children in the Republic of Moldova during the period 1991-2013 reveals a fluctuating evolution, characterized by alternating episodes of increased incidence and periods of significant case decline (Fig. 1).

The highest incidence was recorded in 1991, with a total of approximately 15 cases, representing an early peak in the studied timeframe. After this point, the number of cases progressively decreased until 1994-1995, when a slight in-

crease was observed. Another notable rise occurred around 1999, followed by a relatively steady decline in the early 2000s.

A minimum point on the curve was recorded between 2004 and 2006, when the number of cases remained below 5 per year. This relatively calm period was followed by a sudden resurgence starting in 2007, culminating in a second major epidemiological peak in 2010, when incidence again reached approximately 15 cases. Afterward,

a slight decrease was noted, although the number of cases remained above the previous decade's average until 2013.

This uneven evolution suggests the possible influence of cyclical or contextual contributing factors, such as a lack of national human papillomavirus vaccination program, the absence of active human papillomavirus screening in pregnant women, limited access to pediatric Otolaryngology

care, and potentially underreporting of cases during certain periods.

The annual distribution of medical consultations for recurrent laryngeal papillomatosis throughout the study period is illustrated in the figure (Fig. 2). Trend analysis highlights that the year 2004 recorded the lowest number of cases, while 2010 saw a peak with a total of 15 reported cases, indicating considerable variation in incidence over time.

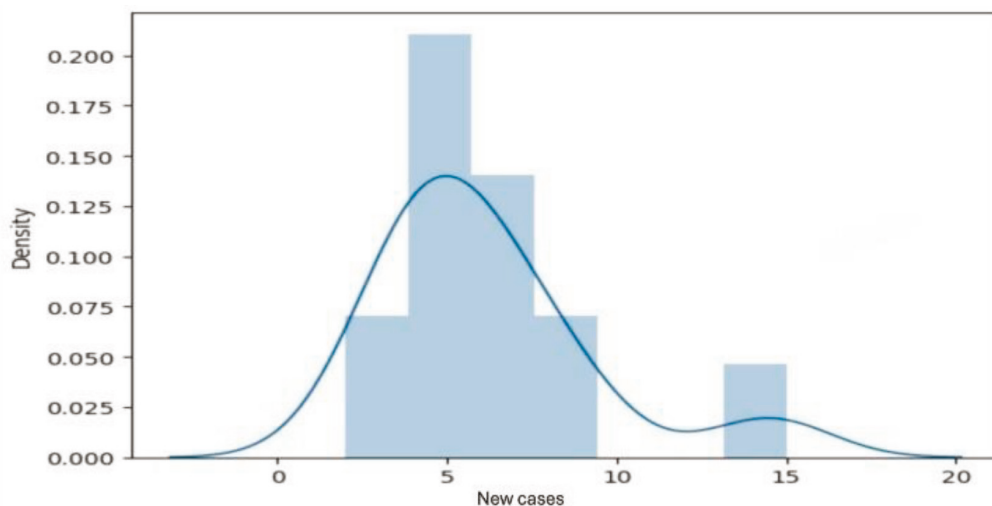
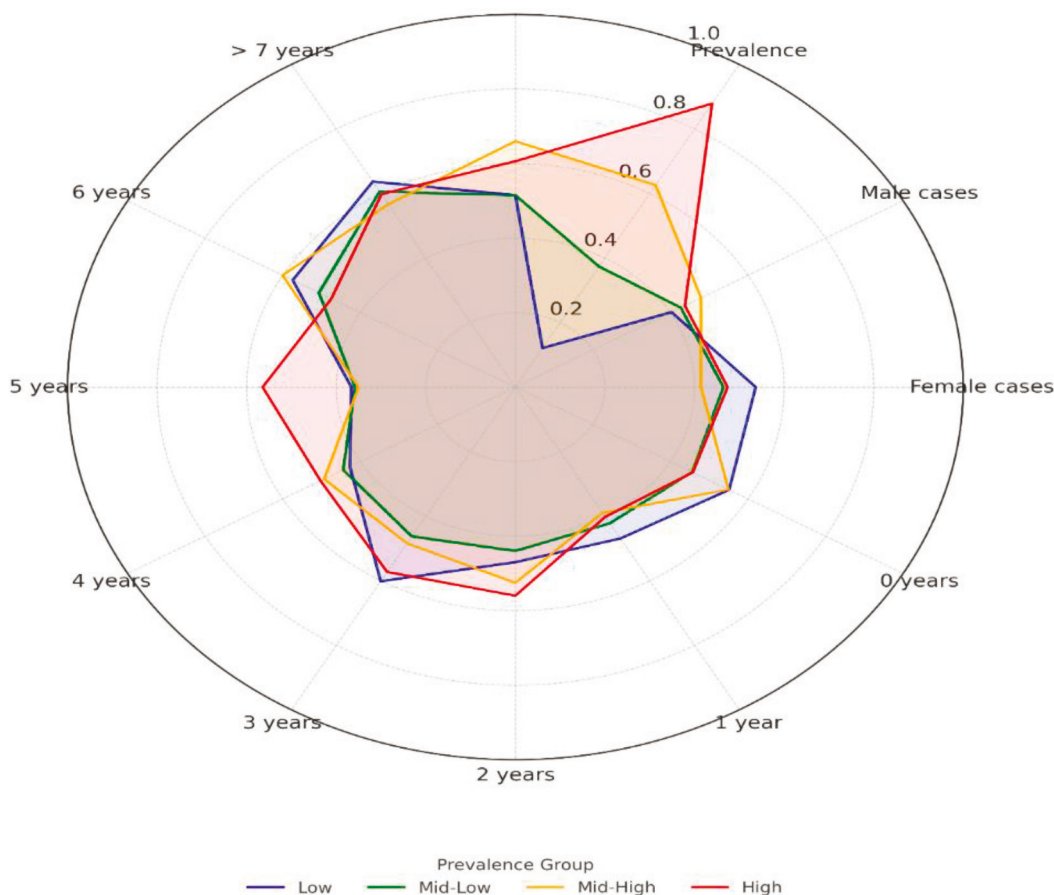


Fig. 3 Annual trend of reported recurrent laryngeal papillomatosis cases (1991–2013).

Note: The distribution of newly reported cases follows a unimodal, right-skewed pattern, with most years clustering around 5 to 7 cases and a small number of outlier years exceeding 15 cases. This suggests a stable baseline incidence, occasionally interrupted by sporadic peaks.

Fig. 4 Correlation between sex, age groups, and the number of new recurrent laryngeal papillomatosis cases

Note: Radar chart illustrating the normalized median values of selected clinical and demographic variables stratified by four prevalence groups of recurrent laryngeal papillomatosis. Prevalence groups were defined by quartiles of the total prevalence distribution: Low (blue), Mid-Low (green), Mid-High (orange), and High (red). Variables include the number of new cases, overall prevalence, sex distribution (male and female), and age-specific representation from 0 to >7 years. The chart highlights distinct patterns across prevalence strata, with higher values in specific age groups and among males in high-prevalence clusters.



The annual progression of recurrent laryngeal papillomatosis cases during the study period is illustrated in the figure (Fig. 3). On average, the number of consultations per year remained below 9 cases. However, specific years – such as 1992 and 2010 – demonstrated a notable increase in frequency, reaching approximately 50% above the average. These isolated spikes, which lack a consistent temporal pattern, may indicate the influence of contextual or environmental factors on disease dynamics. Further investigation into these peaks could yield important insights into epidemiological behavior and inform the development of targeted preventive strategies.

In our study, a strong correlation ($r = 0.86$) was found between “Boys’ Cases” and “New Cases,” indicating that most new referrals originated from male patients (Fig. 4). Additional correlations between the “1 year” and “4 years” age groups suggest a higher frequency of disease onset at these ages, particularly among boys. Meanwhile, a moderate correlation between “Girls’ Cases” and “New Cases” ($r = 0.76$) reflects a relatively balanced incidence across sexes, with slight age-dependent variations.

Additional correlation analysis reveals a notable association ($r = 0.63$) between overall prevalence and the “4 years” age group, confirming a higher frequency of cases at this age among boys. Overall, the data suggest a concentration of cases around the ages of 1 and 4 for males, while in females, referrals tend to be more frequent between 7 and 15 years. These observations may be important for understanding the age and sex distribution of laryngeal papillomatosis onset and can help guide early interventions.

In our study, a strong correlation was observed between the number of new cases and the reported incidence per 100,000 population. However, this association may be considered misleading, as the incidence rate is directly calcu-

lated from the number of new cases. As a result, these two variables are not statistically independent, and the inclusion of incidence in a separate inferential analysis would not provide additional value.

The Shapiro-Wilk normality test applied to the distribution of new cases in our dataset demonstrated a balanced distribution between sexes, with no significant differences in the frequency of referrals. Nonetheless, a sex-based difference was noted regarding the age at presentation, suggesting a potential influence of gender on the timing of disease onset. This aspect merits further investigation in future research.

In our study, the evaluation of errors obtained through the linear regression method supports the validity of the previous interpretations. The estimated difference between the distribution of referrals for boys and girls compared to the total number of new cases is approximately ± 2 cases. Furthermore, the predictive model based on these variables can estimate the number of new cases with a maximum deviation of ± 7 cases from the actual data. However, developing a robust and reliable predictive model for forecasting future cases requires a larger sample size and more extensive data collection.

The analysis of statistical coefficients derived from linear regression in our study reveals that variables related to sex distribution (boys and girls) hold the most significant relevance for analyzing and predicting new cases in the upcoming period. While other variables contribute to a deeper understanding of the studied sample, they do not provide sufficient information for extrapolation to a broader theoretical population. Nonetheless, these variables remain valuable for the specific description and interpretation of the patient group included in our study.

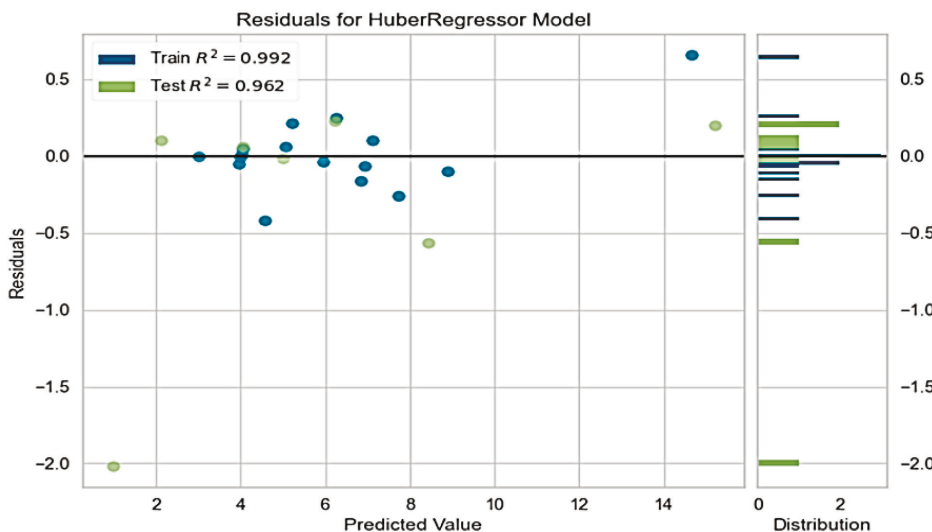


Fig. 5 Exploratory graphical assessment of residual distribution and variance stability in the predictive model

Note: The figure displays residual values plotted against predicted values for both training (blue) and test (green) datasets. The residuals are mostly centered around zero, with minimal dispersion, indicating good model fit and stability. The distribution histogram (right) confirms the symmetrical spread of residuals, with isolated deviations below -2 in the test set.

The error analysis resulting from the linear regression test applied to the predictive model demonstrates an approximately 90% homoscedastic distribution of errors, indicating that the variance of the residuals remains constant

across the range of predicted values (Fig. 5). This consistency in error variance is essential for the validity of linear regression assumptions and ensures that coefficient estimates are efficient and unbiased. Consequently, the model proves

to be robust, minimizing the risk of systematic errors in its predictions. However, for improved accuracy and generalizability, further analyses are recommended to identify any potential outliers or heteroscedasticity within specific data subsets.

Discussion

Recurrent laryngeal papillomatosis is a condition with significant clinical and social implications, especially among children, where disease recurrence and airway involvement can lead to severe complications. The present study, focused on the epidemiological and clinical analysis of pediatric patients in the Republic of Moldova, provides valuable insight into how this disease manifests and progresses within a specific regional context. The results align with recent global observations while also offering new data useful for planning clinical and public health interventions.

One of the most important findings of our study is the confirmation of a higher prevalence of recurrent respiratory papillomatosis (RRP) among boys compared to girls, a trend also reported in the international literature [15, 16]. The biological explanations for this sex difference remain under investigation; however, recent data suggest that immune response and susceptibility to human papillomavirus types 6 and 11 infections may be differently modulated based on sex [17, 18]. These variations may influence both the frequency of infection and the severity of clinical manifestations. Additionally, socio-cultural factors and differential access to healthcare services may play an important role in case detection and reporting, as highlighted by studies emphasizing inequalities within healthcare systems [19].

The average age at disease onset, around 1 and 4 years, aligns with the range reported in numerous multicenter studies [20, 21], suggesting a universal pattern of recurrent laryngeal papillomatosis progression in the pediatric population. These ages coincide with critical periods in immune system development and may reflect a window of increased vulnerability to initial human papillomavirus infection.

The average annual incidence identified in our study – approximately 6 new cases per year – is comparable to values published for regions with similar epidemiological profiles [22, 23]. Annual variability, with significant peaks in certain years (e.g., 1992 and 2010), may be attributed to various factors such as changes in public health policies, variability in case reporting, or actual fluctuations in viral transmission.

An estimated prevalence of 4.2 per 100,000 children is an important indicator highlighting the need for sustained preventive interventions. Although human papillomavirus vaccination remains insufficiently implemented in many regions, it has demonstrated increased efficacy in reducing recurrent laryngeal papillomatosis incidence [24, 25]. Implementing and expanding vaccination programs represent a strategic priority, especially given that recurrent laryngeal papillomatosis is directly associated with infection by human papillomavirus types 6 and 11, which are included in broad-spectrum human papillomavirus vaccines.

The application of linear regression in our study allowed

the identification of statistically significant variables for predicting new case occurrences, particularly those related to sex distribution. This confirms the critical role of demographic factors in disease progression. However, the limited sample size and the absence of detailed data on other factors – such as vaccination status or the presence of comorbidities – limit the capacity to develop complex and robust predictive models [26].

The importance of controlling homoscedasticity and validating models through error analysis is well emphasized in recent methodological studies, which recommend close attention to error variance consistency to ensure accurate estimates and valid interpretations [27]. Our models largely meet these criteria but also highlight the need for further analyses, potentially using machine learning methods or nonlinear models that can better capture data complexity.

Early diagnosis of recurrent laryngeal papillomatosis is crucial for preventing severe complications, which may include airway obstruction, acute respiratory failure, and the need for invasive interventions such as tracheotomy [28]. In this context, educating primary healthcare providers, especially pediatricians and family doctors, about the symptoms and risk factors of recurrent laryngeal papillomatosis is essential to reduce diagnostic delays.

Current clinical management of recurrent laryngeal papillomatosis relies on repetitive surgical interventions; however, the high rate of recurrences necessitates the use of adjuvant therapies. New antiviral and immunomodulatory treatments have shown promising results in reducing recurrence frequency and disease severity [28]. Nonetheless, access to these treatments may be limited in some regions, including the Republic of Moldova, underscoring the need for effective interdisciplinary collaboration and appropriate resource allocation.

Although our study provides important data, the retrospective design entails inherent limitations, such as potential data incompleteness and the inability to control certain variables. Additionally, the lack of detailed information on vaccination history and other environmental factors poses a barrier to comprehensive assessment of causes and risks associated with recurrent laryngeal papillomatosis.

To better understand the involved immunological mechanisms and the predictive potential of biomarkers, prospective and multicenter studies are indispensable [29]. Such studies could integrate molecular, immunological, and epidemiological assessments, providing a solid basis for developing personalized treatment and prevention strategies.

Moreover, expanding human papillomavirus vaccination programs and monitoring their impact on RRP incidence should be a priority in public health policy in the Republic of Moldova and other countries with similar epidemiological profiles [30].

Conclusions

Recurrent laryngeal papillomatosis in children remains a rare but impactful condition, with early onset and clear demographic predispositions that underline the importance of timely diagnosis and multidisciplinary care. Despite

current efforts, significant gaps persist in understanding its pathogenesis and recurrence patterns, warranting further prospective and integrative research. Expanding Human Papillomavirus vaccination coverage stands out as a necessary public health intervention, with the potential to reduce both clinical burden and long-term socioeconomic impact.

Competing interests

None declared.

Authors' contributions

Both authors conceived and designed the study, collected and analyzed the data, and drafted the manuscript. Both authors critically reviewed and approved the final version of the manuscript.

Informed consent for publication

Obtained.

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Ethics approval

Ethical approval was obtained from the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy, under decision no. 9, dated September 20, 2019.

Provenance and peer review

Not commissioned, externally peer review.

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