

# THE ROLE OF THE CERVICOVAGINAL MICROBIOME AND LOCAL IMMUNITY IN HUMAN PAPILOMAVIRUS PERSISTENCE AND PRECANCEROUS CERVICAL CHANGES

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## Annotation

**Background.** This study provides a detailed review of the interactions between the cervicovaginal microbiome, local immune responses, and human papillomavirus infection outcomes.

**Methods.** A literature review was conducted covering the period from 2015 to 2024 using the PubMed, Scopus, Embase, and Google Scholar databases. The search included keywords such as human papillomavirus, cervicovaginal microbiome, dysbiosis, cytokines, cervical cancer, Boolean operators, and Medical Subject Headings terms for search refinement. Inclusion criteria: Peer-reviewed publications in English and Russian focusing on the cervicovaginal microbiome, immune responses, human papillomavirus persistence, and cervical neoplasia; observational studies, clinical trials, and reviews. Exclusion criteria: Non-peer-reviewed sources, gray literature, and studies unrelated to microbiome-immune system interactions or human papillomavirus outcomes.

**Results.** Lactobacillus species, particularly *L. crispatus*, play a key role in maintaining an acidic vaginal environment that modulates local immunity and promotes human papillomavirus clearance. Dysbiosis, characterized by an overgrowth of *Gardnerella*, *Prevotella*, and *Sneathia*, leads to inflammation, disruption of the epithelial barrier, and human papillomavirus persistence. Hormonal fluctuations and environmental factors influence these processes, determining infection outcomes and disease progression.

**Conclusion.** The cervicovaginal microbiome and local immunity are integral to human papillomavirus pathogenesis and cervical cancer prevention.

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## Introduction

Cervical cancer ranks fourth among the leading causes of cancer-related mortality in women worldwide, claiming over 300,000 lives annually. In 95% of cases, it is caused by a persistent infection with high-risk human papillomavirus (HPV) types.<sup>1,2</sup>

Transient HPV infection is spontaneously cleared in 80–90% of cases within 12–24 months. However, persistent infection significantly increases the risk of developing cervical intraepithelial neoplasia (CIN) and invasive cancer.<sup>3</sup>

The cervicovaginal microbiome (CVM) plays a crucial role in shaping the local immune response and influenc-

ing HPV infection outcomes. A healthy CVM is dominated by Lactobacillus species, which create an acidic environment with a low pH and produce antimicrobial compounds that prevent pathogen colonization. In contrast, dysbiosis—characterized by a reduction in Lactobacillus spp. and an increase in anaerobic bacteria such as *Gardnerella vaginalis* and *Prevotellabivia*—is associated with chronic inflammation, immune dysfunction, and HPV persistence.<sup>4</sup>

This review explores the dynamic interplay between the CVM, local immunity, and HPV infection outcomes, while also discussing their clinical and translational implications. The type of review

presented in this article can be classified as a narrative review with a systematic approach, as it covers a broad range of information on the relationship between the cervicovaginal microbiome, local immunity, and HPV persistence while adhering to a structured methodology for literature identification and synthesis.<sup>5</sup>

#### Why We Chose This Type of Review?

This literature review reflects the characteristics of a narrative review due to its broad coverage of the topic, in which key themes and findings are critically analyzed to provide a comprehensive understanding of the subject. The review examines the interaction between microbiome composition, immune responses, and HPV-related outcomes, integrating mechanistic insights with clinical implications in a holistic and interpretative manner. This approach allows the authors to synthesize diverse studies and present a balanced discussion accessible to both researchers and clinicians.<sup>6,7</sup>

At the same time, the review applies a systematic approach in its methodology, as evidenced by the clearly outlined search strategy, inclusion and exclusion criteria, and structured data extraction from peer-reviewed studies. The use of authoritative databases such as PubMed, Scopus, Embase, and Google Scholar, along with the application of Boolean operators and Medical Subject Headings (MeSH) terms, ensures a rigorous and transparent literature selection process. These systematic elements enhance the credibility and reliability of the review by minimizing bias and improving reproducibility.<sup>8,9</sup>

This hybrid approach—a narrative synthesis with systematic elements—enables the article to achieve both breadth and depth in its analysis. It accounts for the heterogeneity of studies in this field while also providing practical recommendations for future research and clinical practice. By combining these methodologies, the review effectively fulfills its purpose, offering a comprehensive yet structured overview of the current state of knowledge regarding the cervicovaginal microbiome and its

role in HPV persistence and precancerous cervical changes.

#### Materials and Methodology

This review was designed to examine the complex interactions between the cervicovaginal microbiome (CVM), local immunity, and human papillomavirus (HPV) persistence, with a particular focus on disease progression to cervical intraepithelial neoplasia (CIN) and cervical cancer. The methodology was structured to ensure a rigorous and systematic approach to identifying, evaluating, and synthesizing relevant literature while allowing for an in-depth narrative discussion.

**Search Strategy.** A comprehensive literature search was conducted in four major databases: PubMed, Scopus, Embase, and Google Scholar. These platforms were selected for their extensive coverage of biomedical and clinical research. The search spanned publications from January 2015 to November 2024, ensuring a thorough review of both foundational and recent studies. To enhance the precision and scope of the search, a combination of keywords and controlled vocabulary terms, including Medical Subject Headings (MeSH), was applied.

The primary search terms included: “HPV” OR “human papillomavirus”, “cervicovaginal microbiome” OR “vaginal microbiota”, “immune modulation” OR “dysbiosis”, “cytokines”, “cervical cancer” OR “cervical intraepithelial neoplasia”

Boolean operators (AND/OR) were used to construct specific search queries. For example:

(“HPV” OR “human papillomavirus”) AND (“cervicovaginal microbiome” OR “vaginal microbiota”) AND (“immune modulation” OR “dysbiosis”).

**Selection Criteria.** Inclusion and exclusion criteria were established to ensure the selection of high-quality and relevant studies:

**Inclusion Criteria:** Peer-reviewed articles published in English.

- Studies focusing on the cervicovaginal microbiome, immune responses, HPV persistence, or cervical neoplasia.

- Observational studies, clinical trials, systematic reviews, and meta-analyses.

- Studies utilizing microbiome profiling, cytokine analysis, or other molecular methods related to HPV-associated pathogenesis.

Exclusion Criteria: Non-peer-reviewed sources, gray literature, conference abstracts, and editorial articles.

- Studies not related to microbiome-immune system interactions or HPV infection outcomes.

- Articles with insufficient methodological details or small sample sizes, which could reduce the reliability of findings.

**Study Selection Process.** Three independent reviewers screened the titles and abstracts of all retrieved articles to assess their relevance. The full texts of potentially eligible studies were then reviewed to confirm their adherence to the inclusion criteria. Any discrepancies among reviewers were resolved through discussion and consensus.

To ensure consistency in data extraction, a standardized data collection form was used, which included:

- Study design and methodology.
- Characteristics of the study population.
- Microbiome assessment methods (e.g., 16S rRNA sequencing, metagenomics).
- Analyzed immune markers or cytokines.
- Key findings related to HPV persistence, immune modulation, or microbiome composition.

**Data Synthesis and Analysis.** Extracted data were synthesized in a descriptive format, considering the heterogeneity of study designs, populations, and microbiome assessment methods. Although meta-analytic methods were not applied, recurring patterns and trends were identified and discussed within the context of existing literature. Special attention was given to mechanisms, clinical implications, and translational potential for HPV-related disease management.

**Quality Assessment.** To ensure the reliability of the included studies, a quality assessment was conducted using adapted criteria from established tools, such as the Newcastle-Ottawa Scale (NOS) for observational studies and the Cochrane Risk of Bias tool for clinical trials. Studies with significant methodological weaknesses were excluded from the review.

**Ethical approval.** This study did not involve primary data collection or the participation of human or animal subjects, and therefore, ethical approval was not required.

## Results

**Cervicovaginal Microbiome Under Physiological Conditions.** A healthy cervicovaginal microbiome (CVM) is dominated by *Lactobacillus spp.*, particularly *Lactobacillus crispatus*, *L. gasseri*, and *L. jensenii*. *Lactobacillus spp.* play a crucial role in maintaining vaginal microbiota homeostasis.<sup>5</sup> They produce lactic acid, which lowers vaginal pH, creating an unfavorable environment for pathogenic microorganisms. This antimicrobial barrier suppresses inflammatory processes and reduces infection rates, including HPV infection.<sup>10,11</sup>

In addition to lactic acid production, *Lactobacillus spp.* synthesize hydrogen peroxide and bacteriocins, which further inhibit pathogenic bacterial growth and provide additional protective effects.<sup>3,12</sup> These bacteria also modulate immune responses by interacting with epithelial cells, enhancing cytokine production and strengthening mucosal defense. One of their key functions is adherence to vaginal epithelial cells, which prevents the attachment of other microbes, a crucial step in infection prevention.<sup>13</sup>

*Lactobacillus spp.* are the primary producers of L- and D-lactic acid isomers, which help maintain vaginal pH below 4.5. Additionally, vaginal epithelial cells contribute approximately 20% to L-lactic acid production.<sup>14,15</sup>

Thus, the dominant *Lactobacillus* species determines the level of protection provided by the vaginal ecosystem.

Key factors influencing the vaginal microenvironment, such as pH regulation, the role of lactic acid bacteria, microbial metabolites, and local inflammatory responses, collectively contribute to maintaining vaginal health.<sup>3,16,17</sup>

*Microbiome Alterations and HPV Persistence.* There is no reliable direct evidence demonstrating how vaginal microbiome alterations affect local immune function.<sup>4</sup> However, an increasing body of literature suggests that vaginal microbiota contributes to the production of pro- and anti-inflammatory cytokines. IL-1 $\alpha$ , IL-1 $\beta$ , and IL-8 are key pro-inflammatory cytokines activated in bacterial vaginosis (BV) and HPV infection. IL-6 plays a role in inflammation and the immune response to HPV, with its increased expression being associated with the progression of precancerous and malignant changes. IL-10, an immunosuppressive cytokine, is elevated in HPV persistence and neoplasia development, with its expression induced by HPV oncoproteins E2, E6, and E7. IL-12 is involved in antiviral immune activation by stimulating the Th1 response, and its reduced levels in CST-IV microbiomes may contribute to chronic HPV infection. IL-17 is elevated in women with HPV infection, potentially playing a role in systemic but not local inflammation, promoting viral persistence. IL-36 $\gamma$  is associated with inflammation and cervical cancer, but its production is not linked to the vaginal microbiome; instead, it is driven by epithelial cell activation.<sup>18,19</sup>

Dysbiosis, characterized by a reduction in *Lactobacillus* spp. and an increase in anaerobic bacteria, such as *Gardnerella* and *Prevotella* spp., creates conditions that favor HPV persistence. Dysbiotic microbiomes elevate pro-inflammatory cytokine levels (IL-1 $\beta$  and TNF- $\alpha$ ), disrupting immune homeostasis.<sup>20</sup>

Pathogenic bacteria compromise epithelial integrity, facilitating viral entry and persistence. Dysbiosis also suppresses innate immune responses, allowing HPV to evade detection.<sup>21</sup> Studies have linked *L. crispatus*-dominated mi-

crobiomes to reduced HPV persistence and a lower risk of cervical cancer.<sup>4</sup> Recent research highlights a significant association between immune status, viral infection, and the vaginal microbiome, which influences lower genital tract immunity.<sup>22-24</sup>

Studies comparing CST-I (*Lactobacillus crispatus*) and CST-III (*Lactobacillus iners*) with CST-IV (dominated by *Prevotellaamniai*, *Mobiluncusmulieris*, and *Sneathia* spp.) show CST-IV induces higher pro-inflammatory cytokine production (IL-1 $\alpha$ , IL-1 $\beta$ , IL-8), highlighting its role in cervicovaginal immune modulation.<sup>13,25,26</sup>

Recent cross-sectional studies have focused on characterizing the cervicovaginal microbiome in women with cervical lesions. A study in the United Kingdom involving 169 women (20 healthy controls, 52 with low-grade squamous intraepithelial lesions (LSIL), 92 with high-grade lesions (HSIL), and 5 with invasive cervical cancer) revealed that increased CIN severity correlated with greater CVM diversity and a reduced relative abundance of *Lactobacillus* spp. A stepwise increase in the prevalence of CST-IV was observed with disease severity, rising from 10% in healthy controls to significantly higher levels in LSIL, HSIL, and invasive cervical cancer cases. Higher levels of *Sneathiasanguinegens*, *Anaerococcustetradius*, and *Peptostreptococcus anaerobius* and lower levels of *Lactobacillus jensenii* were found in HSIL compared to LSIL.<sup>4</sup>

A study in Mexican women confirmed these findings, linking greater CVM diversity and increased *Sneathia* spp. and *Fusobacterium* spp. with more severe disease. High *Fusobacterium* spp. proportions correlated with increased IL-4 and TGF-1 $\beta$  mRNA levels, potentially enabling HPV immune evasion.<sup>23</sup>

*Hormonal Influence on the Microbiome.* Hormonal changes significantly impact the vaginal microbiome and HPV persistence. Estrogens promote *Lactobacillus* spp. growth, enhancing glyco-

homeostasis.<sup>27</sup> Menopause-related estrogen decline leads to dysbiosis, increased vaginal pH, and prolonged HPV persistence.<sup>28</sup>

Vaginal microbiome changes occur throughout a woman's life and have a significant impact on quality of life.<sup>28</sup> These changes are influenced by hormonal fluctuations, physiological transitions, and external factors, playing a key role in modulating local immunity and determining susceptibility to infections.<sup>16,29</sup>

According to the study by *Kaur et al.*<sup>30</sup>, puberty is characterized by high bacterial diversity, whereas in reproductive age, low bacterial diversity corresponds to a healthy vaginal flora. Scientists explain these dynamics of the cervicovaginal microbiome by the increase in circulating estrogen levels only in the late stages of puberty, leading to increased glycogen production in vaginal epithelial cells, which serves as a nutrient source for lactic acid bacteria such as *Lactobacillus*. The production of hydrogen peroxide and lactic acid inhibits the growth of other bacterial species.<sup>30,31</sup> (Table 1).

In early adolescence, when estrogen and progesterone levels remain low, the vaginal microbiome is characterized by high alpha diversity, including the predominance of *Aspergillus*, *Actinobacteria*, and various bacterial genera such as *Prevotella*, *Bacteroides*, *Gastrodia*, anaerobes, and small populations of *Bacteroides* and *Lactobacillus*. With the development of gonads and in late adolescence, the vaginal microbiome becomes predominantly dominated by thick-walled bacteria. Simultaneously, increasing levels of sex hormones contribute to the thickening of the vaginal epithelium and the accumulation of glycogen, providing an important nutrient source for the growth and reproduction of microorganisms. This period is critical for vaginal health formation, and preventive measures such as HPV vaccination and educational programs are of utmost importance.<sup>11,20,31</sup> (Table 1).

During menstruation, the vaginal microbiome undergoes significant alter-

tations due to increased pH and microbial diversity. The neutral pH of menstrual blood (7.2–7.4) attenuates the antimicrobial properties of lactic acid, facilitating the proliferation of anaerobic bacteria such as *Streptococcus* and *Gardnerella*, which utilize iron as a growth factor. In *Lactobacillus*-dominant microbiomes, neutrophil gelatinase-associated lipocalin (NGAL) restricts iron-dependent bacterial expansion.<sup>31</sup> As the menstrual cycle progresses to the follicular phase, rising estrogen levels induce epithelial proliferation, enhance glycogen deposition, and restore an acidic environment, promoting *Lactobacillus* dominance and limiting anaerobic bacterial overgrowth.

During pregnancy, enhanced *Lactobacillus* predominance provides protective benefits, while dysbiosis is linked to complications such as preterm birth and miscarriage.<sup>22,23</sup> Postpartum hormonal shifts increase susceptibility to infections like endometritis (Table 1).

In menopause, estrogen levels decrease while follicle-stimulating hormone (FSH) levels increase, leading to a reduction in *Lactobacillus* concentration and promoting the growth of anaerobic bacteria in the vaginal environment.<sup>30</sup> These changes can vary among women. In postmenopause, the microbiota primarily includes *Gardnerella vaginalis*, *Ureaplasma urealyticum*, *Candida albicans*, and *Prevotella spp.*, while the proportion of *Lactobacillus* progressively declines. The reduction of *Lactobacillus* in postmenopausal women is a normal physiological process<sup>32,33</sup>; however, these changes can negatively impact sexual health due to the development of vulvovaginal atrophy and vaginal dryness (Table 1).

A study by *Mirmonsef et al.*<sup>33</sup> found a strong correlation between *Lactobacillus jensenii* and glycogen levels, with *Lactobacillus iners* more prevalent in premenopausal women. Postmenopausal women exhibited lower glycogen and higher vaginal pH. Some evidence suggests rectal *Lactobacilli* could act as a reservoir for restoring vaginal microbiota balance in postmenopausal women.<sup>33,34</sup> (Table 1).

**Table 1.**  
Microbiome of the cervix and vagina at different stages of a woman's life

Life stage	Dominant microbiota	Key characteristics	Influence in factors	Clinical significance
Childhood (prepuberty)	Diverse microbiota: Prevotella, Streptococcus, Clostridium, Bacteroides, Aspergillus, Actinobacteria	High alpha diversity; lack of dominance of Lactobacillus. pH neutral or slightly alkaline <sup>30</sup>	Low estrogen levels, immature immune system, limited amount of glycogen in the vaginal epithelium <sup>30</sup>	Increased susceptibility to infections due to the lack of protective properties of Lactobacillus spp.; limited local immunity.
Adolescence	Transient microbiota: Prevotella, Streptococcus, mixed anaerobes; dominance of Lactobacillus spp begins. <sup>30</sup>	The onset of hormonal changes stimulates the production of glycogen, which promotes Lactobacillus colonization. Increased epithelial thickness <sup>16</sup>	Increased levels of estrogen and progesterone during puberty, the onset of the menstrual cycle and sexual activity <sup>30</sup>	Shift to Lactobacillus dominance improves protection; important period for HPV vaccination to prevent persistent infections <sup>35</sup>
Reproductive age	Dominance of Lactobacillus: L. crispatus, L. jensenii, L. gasseri <sup>10</sup>	Low microbial diversity; dominance of Lactobacillus spp. forms an acidic environment (pH < 4.5). Production of lactic acid and antimicrobial compounds <sup>14</sup>	High estrogen levels, stable glycogen production, menstrual cycles and sexual activity <sup>30</sup>	An optimal CVM environment provides protection against HPV and other STIs. Dysbiosis at this stage is associated with an increased risk of HPV persistence and CIN <sup>4</sup>
Pregnancy	Dominance of Lactobacillus: L. crispatus, L. gasseri <sup>24</sup>	Increased dominance of Lactobacillus spp. and further decline in microbial diversity. Lower pH (<4.0) enhances anti microbial protection <sup>10</sup>	High levels of estrogen and progesterone; immunomodulation to maintain pregnancy <sup>24</sup>	Reduced risk of infections due to the pronounced dominance of Lactobacillus. Dysbiosis during pregnancy increases the risk of preterm birth and adverse outcomes <sup>23</sup>
Postpartum period	Mixed microbiota: decreased number of Lactobacillus spp.; dominance of Gardnerella, Prevotella and anaerobes <sup>10</sup>	Reduced levels of Lactobacillus spp. and increased microbial diversity due to hormonal changes and possible physical trauma after child birth. Increased inflammation <sup>4</sup>	A sharp decrease in the level of estrogen and progesterone; tissue repair processes; risk of postpartum infections <sup>23</sup>	High risk of postpartum infections (eg, endometritis, vaginitis). Monitoring of dysbiosis is necessary for recovery and reduction of complications <sup>24</sup>

Peri menopause	Decrease in the number of <i>Lactobacillus</i> spp.; increased diversity with dominance of <i>Gardnerella</i> , <i>Prevotella</i> and anaerobes <sup>28</sup>	Reduced dominance of <i>Lactobacillus</i> ; increased microbial diversity; increase in pH (> 4.5). Possible dysbiosis <sup>24</sup>	Fluctuating estrogen levels, irregular menstrual cycles, and stress-induced hormonal changes <sup>27</sup>	Dysbiosis and decreased levels of <i>Lactobacillus</i> spp. increase the risk of vaginal infections and persistence of HPV. <sup>36</sup>
Post menopause	Decrease in the number of <i>Lactobacillus</i> spp.; dominance of <i>Gardnerella</i> , <i>Prevotella</i> , <i>Candida</i> , <i>Ureaplasma</i> , anaerobes <sup>34</sup>	Increased microbial diversity; increase in pH (5.0–7.0). Vaginal dryness, atrophy and increased susceptibility to infections <sup>28</sup>	Decreased estrogen levels, decreased glycogen production, thinning of the vaginal epithelium <sup>16</sup>	Increased risk of recurrent infections, including bacterial vaginosis and candidiasis. Increased vulnerability to HPV-associated diseases and cervical cancer <sup>27</sup>

*Key findings on the cervicovaginal microbiome and its impact on HPV-associated diseases.* The cervicovaginal microbiome plays a central role in modulating local immunity, influencing the persistence of the human papillomavirus, and determining the progression of cervical intraepithelial neoplasia. The protective role of *Lactobacillus* species, particularly *Lactobacillus crispatus*, is well-studied. These bacteria maintain a low vaginal pH (<4.5), produce antimicrobial compounds, and enhance immune responses, which help reduce HPV persistence and associated risks.<sup>10,14</sup> Research consistently shows that a microbiome dominated by *Lactobacillus* spp. is associated with favorable outcomes, including reduced inflammation and improved epithelial barrier integrity.<sup>4,22</sup> (Table 2).

In contrast, dysbiosis is characterized by an overgrowth of anaerobic bacteria such as *Gardnerellavaginalis*, *Prevotellabivia*, and *Sneathia* spp., leading to chronic inflammation and disruption of the epithelial barrier. This condition creates a microenvironment conducive to HPV persistence and disease progression. Studies have demonstrated that dysbiosis is closely linked to the severity of CIN, with more microbial diversity in later stages of lesions and a reduction in *Lactobacillus* spp.<sup>20</sup> (Table 2).

Hormonal fluctuations significantly affect the cervicovaginal microbiome. Estrogen helps maintain a healthy vaginal microbiome during reproductive years by increasing glycogen availability and stimulating the growth of *Lactobacillus*. However, during menopause, this balance is disrupted due to a decrease in estrogen levels, an increase in vaginal pH, and greater microbial diversity, which may contribute to HPV persistence and the progression of CIN.<sup>26,27</sup> (Table 2).

Clinical studies further highlight the role of the microbiome in the progression from HPV infection to cervical cancer. Women with CIN and invasive cancer show a significant reduction in *Lactobacillus* spp. and an increase in anaerobic bacteria compared to healthy controls. This state of dysbiosis is associated with elevated levels of pro-inflammatory cytokines and reduced immune response effectiveness, underscoring the critical role of the microbiome in disease progression.<sup>29</sup>

Emerging therapeutic approaches aim to use this knowledge for clinical benefit. Probiotic treatments targeting the restoration of *Lactobacillus* spp. show promise in reducing inflammation, improving mucosal immunity, and accelerating HPV clearance.<sup>29,37</sup> Personalized treatment strategies, in-

cluding microbiome profiling, are gaining popularity, offering the possibility of early identification of high-risk patients and individualized interventions. Immunomodulatory therapies, especially those targeting cytokine pathways, represent a promising adjunct to microbiome-oriented methods<sup>35,37-39</sup> (Table 2).

These findings emphasize the im-

portance of the cervicovaginal microbiome in HPV-related pathogenesis and open opportunities for the development of new preventive and therapeutic strategies. Future research should focus on studying the protective role of individual bacterial strains, the interaction of the microbiome with the virome, and the development of interventions that combine microbiome restoration with enhanced immune responses.

**Table 2.**  
Factors influencing the cervicovaginal microbiome

Aspects	Key findings	Supporting data (links to literature sources)
The protective role of <i>Lactobacillus spp.</i>	The predominance of <i>L.crispatus</i> creates an acidic environment (pH <4.5), modulates immunity and reduces the persistence of HPV.	4,10,11
Impact of dysbiosis	Dysbiosis, characterized by an increase in <i>Gardnerella</i> , <i>Prevotella</i> , and <i>Sneathia</i> , causes inflammation and epithelial disruption, promoting HPV persistence.	4,23,24
Hormonal influence	Estrogen promotes <i>Lactobacillus</i> growth and glycogen availability; menopause increases pH and microbial diversity, increasing HPV persistence.	27,28,30
Microbiome in CIN and cancer	Increased diversity of cervical and vaginal microbiota with a decrease in <i>Lactobacillus spp.</i> and an increase in anaerobes correlates with higher severity of CIN.	4,23
Promising therapeutic approaches	Probiotics targeting <i>Lactobacillus</i> restoration, immunomodulation and microbiome profiling for personalized treatment strategies.	35,36,38,39

**Strengths** This manuscript has significant strengths, beginning with its comprehensive coverage of the relationship between the cervicovaginal microbiome, local immunity, and HPV persistence. The integration of research findings from the past two decades provides a deep and up-to-date examination of the topic, including both basic studies and recent advancements. The discussion expertly connects basic science with clinical practice, offering a multidisciplinary perspective that is valuable for researchers, clinicians, and public health specialists.

One of the notable merits is the manuscript's emphasis on translational significance, highlighting the potential of microbiome-based therapies and personalized medicine in managing HPV-associated diseases. The balanced approach of considering both protective and pathogenic microbiota provides a nuanced understanding of their role in HPV persistence and the progression of cervical cancer. Furthermore, the focus on future research directions, such as longitudinal studies and therapeutic innovations, underscores the manuscript's forward-looking nature, making it a

valuable resource for future research.

By addressing practical applications alongside mechanistic aspects, the manuscript appeals to a wide audience and aligns with current trends in precision medicine. The integration of recent data and the provision of practical recommendations for microbiome profiling and therapeutic interventions further strengthen the manuscript's impact. This comprehensive and interdisciplinary approach solidifies the manuscript as a significant contribution to the field.

**Limitations.** Despite numerous strengths, the manuscript has limitations that deserve attention. As a review article, it largely relies on existing literature and does not provide original experimental or clinical data, which limits its ability to definitively resolve unresolved questions. The reliance on peer-reviewed studies introduces the possibility of publication bias, which may exclude relevant results from non-peer-reviewed sources or new research.

The heterogeneity of the studies considered, including differences in methodologies, sample sizes, and definitions of dysbiosis, creates challenges in forming consistent and universally applicable conclusions. Similarly, the manuscript may not fully reflect the dynamics of the microbiome in resource-limited settings, where the burden of HPV-associated diseases is highest and microbiome profiles may differ significantly.

Although the virome is recognized as an area of interest, its discussion is underdeveloped compared to the bacterial microbiome, leaving an important dimension of HPV-microbiome interaction insufficiently explored. The lack of meta-analyses in this area limits the manuscript's ability to quantitatively synthesize data and draw statistically supported conclusions.

Despite the promising therapeutic strategies suggested, the lack of specificity regarding the most effective probiotic strains or immunomodulatory approaches limits their immediate applicability in clinical practice. These lim-

itations point to areas for improvement in future updates or additional research, which could enhance the manuscript's overall impact and provide a stronger foundation for advancing research and patient care in this field.

**What's known?** Extensive research shows that the cervicovaginal microbiome is crucial for maintaining vaginal health and regulating local immune responses. A *Lactobacillus*-dominated environment helps preserve an acidic pH that prevents pathogenic growth and supports effective immune defenses. In contrast, dysbiosis—characterized by a decrease in *Lactobacillus* spp. and an increase in anaerobic bacteria—has been linked to chronic inflammation, impaired mucosal immunity, and the persistence of high-risk human papillomavirus infections. Studies, including those from Central Asia, further emphasize how hormonal fluctuations affect microbiome composition and contribute to the development of cervical intraepithelial neoplasia and cervical cancer.

**What's new?** Our manuscript enhances current understanding by offering an integrated synthesis of mechanistic insights and clinical correlations tailored to Kazakhstan's unique demographic and epidemiological setting. It unravels the complex interactions among hormonal changes, local immunity, and the cervicovaginal microbiome, while also identifying promising targets for therapeutic intervention. By proposing innovative strategies such as targeted probiotic and immunomodulatory therapies, our work lays a solid foundation for personalized approaches to managing HPV-related conditions, marking a significant step forward in the prevention, early detection, and treatment of cervical pathology.

### Conclusion

The cervicovaginal microbiome and local immunity play a key role in determining the persistence of human papillomavirus and the progression to cervical intraepithelial neoplasia and cervical cancer. A healthy microbiome, dominat-

ed by *Lactobacillus* species, creates an environment that protects against HPV persistence by maintaining a slightly acidic vaginal pH, producing antimicrobial compounds, and modulating immune responses. In contrast, dysbiosis, characterized by reduced levels of *Lactobacillus* spp. and an overgrowth of anaerobic bacteria (such as *Gardnerella*, *Prevotella*, and *Sneathia*), promotes inflammation, epithelial barrier disruption, and weakened immune defense, creating conditions favorable for HPV persistence and progression to precancerous and cancerous lesions.

Understanding the complex interactions between the microbiome, virome, and host immunity opens new opportunities for improving the prevention and treatment of HPV-related diseases. Therapeutic strategies aimed at restoring microbial balance, such as the use of probiotics and prebiotics, hold significant potential. These interventions could contribute to HPV elimination, reduce inflammation, and prevent the progression of precancerous lesions. Investigating immunomodulatory therapies and the impact of hormonal changes on the microbiome at different stages of life may further improve outcomes for women at risk.

Future research should focus on longitudinal studies to better understand the dynamic relationships between the microbiome and HPV over time. Investigating the role of individual bacterial strains and their protective or harmful effects is crucial for developing targeted therapies. Similarly, studying interactions between bacterial communities and the virome could uncover new factors influencing disease progression or resolution. Gathering data on the impact of standard CIN treatments on the microbiome may help develop post-therapeutic interventions aimed at restoring balance and preventing recurrences.

Clinically, integrating microbiome profiling into diagnostics and treatment planning may enable early identification of individuals at heightened risk of HPV persistence and CIN progression.

Personalized therapeutic approaches, including targeted probiotics, immunomodulators, and hormone-based interventions, could enhance patient outcomes. Preventive strategies, such as HPV vaccination, early screening, and education, remain crucial, particularly for high-risk populations.

In conclusion, the cervicovaginal microbiome is a critical determinant of HPV persistence and cervical carcinogenesis. Advancing microbiome-based diagnostics and therapeutics holds promise for improving prevention, early detection, and treatment strategies, ultimately reducing the burden of HPV-associated diseases and enhancing women's health.

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**Authors' Contributions.** Y.K. – Conceptualized and designed the study, supervised the research process, and provided critical revisions to ensure scientific rigor. T.U. – Led the research project, coordinated data collection and processing, and contributed substantially to the overall study design, performed the final editing of the manuscript. G.A. – Collected and prepared the data, performed primary data processing, and assisted in verifying the material. G.B. – Conducted the literature review, contributed to the interpretation of the data, and played a key role in drafting the manuscript. K.K. – Participated in the

literature review and data analysis, and contributed to the writing of the introduction and discussion sections. N.K. – Performed statistical processing and analysis of the material, and contributed to writing the Materials and Methods and Results sections. M.T. – Provided expert guidance throughout the study, critically

revised the manuscript for intellectual content, and approved the final version. B.I. – Assisted in data synthesis and interpretation, contributed to the drafting of the manuscript, and approved the final version. All authors have read and approved the final version of the manuscript.

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