THE VAGINAL MICROBIOME AND HUMAN PAPILLOMAVIRUS INFECTION: FROM LACTOBACILLARY PROTECTION TO DYSBIOSIS AND THERAPEUTIC PROSPECTS. A NARRATIVE REVIEW

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Abstract: The vaginal microbiome has emerged as an important cofactor in the natural history of human papillomavirus infection and cervical carcinogenesis. Under physiological conditions, the vaginal environment is dominated by a small number of *Lactobacillus species* that maintain a low pH through lactic-acid production and restrain potential pathogens. Loss of this lactobacillary dominance, a state known as dysbiosis, has been associated with the acquisition, persistence and progression of human papillomavirus infection. This narrative review summarises the current understanding of this relationship across four themes: the protective mechanisms of lactobacilli, the features of dysbiosis and its association with infection, the proposed mechanisms linking dysbiosis and infection and the emerging therapeutic prospects. The evidence consistently shows that a lactobacilli-dominated state is more frequent in uninfected women, whereas a community rich in anaerobes such as *Gardnerella vaginalis, Prevotella, Atopobium* and *Sneathia* predominates among the infected. The direction of causation remains unresolved, since dysbiosis may facilitate viral acquisition while the virus may itself reshape the microbiome, a bidirectional, self-reinforcing relationship is increasingly favoured. The species *Lactobacillus iners* occupies an ambiguous position, being associated with both health and transitional states. Therapeutic restoration of a lactobacilli-dominated community, through probiotics and, more recently, vaginal microbiota transplantation, represents a promising but still preliminary approach for supporting viral clearanceIt is recommended that microbiome assessment, including by targeted molecular assays suitable for routine laboratories, be evaluated for use alongside existing cervical screening and risk-stratification methods, and that microbiome-directed interventions be examined in controlled studies. The literature was identified through searches of PubMed and Google Scholar and was limited to peer-reviewed, indexed journals. This review is intended to provide an integrated synthesis for clinicians and laboratory specialists in the region.
Keywords: vaginal microbiome, human papillomavirus, *Lactobacillus species*, dysbiosis, probiotics

1. INTRODUCTION

Persistent infection with a high-risk genotype of human papillomavirus is the principal cause of cervical cancer. Since only a minority of infections progress, attention has increasingly turned to the cofactors that influence whether an infection persists and advances (Doorbar, 2006). Among these, the vaginal microbiome has attracted particular interest over the past decade. The vagina harbours a complex microbial community that, in the healthy state, performs a protective role, and disturbance of this community has been associated with a range of adverse reproductive and oncological outcomes (Amabebe & Anumba, 2018). A growing body of evidence links the composition of this microbiome to the natural history of human papillomavirus infection, raising the possibility that microbiome assessment, and ultimately microbiome modification, may contribute to cervical cancer prevention (Santella et al., 2022; Sharifian et al., 2023).

This review summarises the current understanding of the relationship between the vaginal microbiome and human papillomavirus infection. It addresses, in turn, the protective mechanisms of lactobacilli, the characteristics of dysbiosis and its association with infection, the mechanisms proposed to link the two, and the therapeutic prospects that follow from this relationship.

2. THE PROTECTIVE ROLE OF LACTOBACILLI

In the majority of women of reproductive age, the vaginal microbiome is dominated by a small number of *Lactobacillus species*, principally *L. crispatus, L. iners, L. gasseri* and *L. jensenii* (Amabebe & Anumba, 2018). These organisms ferment glycogen released from the oestrogenised vaginal epithelium into lactic acid, maintaining a pH below 4.5 that is inhospitable to many potential pathogens (Tachedjian et al., 2017). Lactic acid itself, particularly the D-isomer produced by certain lactobacilli, has direct microbicidal and immunomodulatory properties and contributes to the integrity of the mucosal barrier (Witkin et al., 2013; O'Hanlon et al., 2011). The dominance of lactobacilli is so characteristic of vaginal health that its maintenance has been described as the default protective state of the lower genital tract (Witkin & Linhares, 2017). Beyond acidification, lactobacilli produce bacteriocins and hydrogen peroxide, compete with pathogens for adhesion sites and nutrients, and modulate the local innate immune response, collectively limiting the establishment of infection.

3. DYSBIOSIS AND ITS ASSOCIATION WITH HPV INFECTION

A reduction in the relative abundance of lactobacilli is accompanied by a shift towards a more diverse, anaerobe-dominated community, a state clinically recognized as bacterial vaginosis, or more generally as dysbiosis. This state is characterised by the overgrowth of organisms such as *Gardnerella vaginalis, Prevotella, Atopobium, Megasphaera, Sneathia* and *Fusobacterium* (Borgogna et al., 2020). A substantial and consistent body of cross-sectional evidence links this dysbiotic state to human papillomavirus infection. Lin et al. (2022) reported high-risk infection considerably more often in women whose flora was dominated by *Gardnerella vaginalis* than in those dominated by *Lactobacillus species*, and similar associations have been reported across diverse populations (Lee et al., 2013; Qi et al., 2024). A reduced abundance of lactobacilli and an increased diversity of anaerobic taxa have been observed not only in infected women but also, in several studies, in association with increasing severity of cervical intraepithelial neoplasia, suggesting that the degree of dysbiosis may parallel the degree of disease (Usyk et al., 2022; Castanheira et al., 2021).

The position of *Lactobacillus iners* within this framework is ambiguous. Unlike *L. crispatus*, which is robustly associated with a stable protective state, *L. iners* is found both in health and in communities undergoing transition towards dysbiosis, and its presence has been associated with a less stable microbiome and, in some studies, with infection and cervical abnormality (Zheng et al., 2021; Macklaim et al., 2013). This ambiguity cautions against treating all lactobacilli as equivalent and indicates that the species composition, not merely the proportion, of the lactobacillary flora is relevant.

4. MECHANISMS LINKING THE MICROBIOME AND HPV

Several mechanisms have been proposed to explain the association between dysbiosis and human papillomavirus infection, and they are not mutually exclusive. Anaerobic organisms such as *Gardnerella vaginalis* produce sialidases and other enzymes that degrade the protective cervicovaginal mucus and disrupt the epithelial barrier, facilitating viral access to the basal cells in which infection is established (Anton et al., 2022). Dysbiosis is accompanied by a pro-inflammatory mucosal environment and by oxidative stress, which may promote DNA damage and the integration of viral genes into the host genome (Castanheira et al., 2021). The loss of the protective effects of lactic acid and bacteriocins removes a barrier to viral persistence, while the depletion of lactobacilli also diminishes the immunomodulatory signals through which these organisms normally restrain local inflammation.

The direction of causation, however, remains one of the central unresolved questions in this field, and the available evidence increasingly suggests that the relationship operates in both directions rather than along a single causal axis.

Dysbiosis as a facilitator of infection

The first direction holds that a pre-existing dysbiotic environment predisposes to the acquisition and persistence of human papillomavirus. In this model, the loss of lactobacillary protection precedes infection and creates conditions favourable to it. The elevated vaginal pH that accompanies dysbiosis, together with the enzymatic degradation of the mucus layer by anaerobic organisms, exposes the basal epithelial cells that the virus must reach in order to establish infection (Anton et al., 2022). The chronic, low-grade inflammation characteristic of the dysbiotic state recruits activated immune cells whose turnover and cytokine output may paradoxically support viral entry and the survival of infected cells, while the accompanying oxidative stress promotes the DNA damage and genomic instability that favour the integration of viral oncogenes (Castanheira et al., 2021). Consistent with this sequence, prospective data indicate that women whose vaginal flora is depleted of lactobacilli and dominated by anaerobes are at greater risk of subsequently acquiring infection and of failing to clear it, and that bacterial vaginosis is associated with both prevalent and incident infection across populations (Usyk et al., 2022; Qi et al., 2024). On this interpretation, the microbiome is a factor that precedes human papillomavirus infection and shapes its natural history.

HPV as a modifier of the microbiome

The second direction reverses this sequence and holds that the virus actively reshapes the microbial community in its own favour. The most direct mechanistic evidence comes from Lebeau et al. (2022), who demonstrated that the viral E7 oncoprotein, acting through the NF-κB and Wnt/β-catenin signalling pathways, down-regulates a family of host innate antimicrobial peptides in the cervicovaginal mucosa. Crucially, these peptides serve as a source of amino acids for lactobacilli, their suppression therefore deprives the lactobacilli of an essential nutrient and undermines the very population that would otherwise maintain a protective, acidic environment. By this route the infection does not merely coexist with dysbiosis but actively promotes it, converting a lactobacilli-dominated community into one permissive to anaerobic overgrowth. Additional viral effects on epithelial differentiation, mucin production and local immune signalling may reinforce this shift, so that the established infection progressively remodels its own microbial niche.

A bidirectional, self-reinforcing relationship

Taken together, these two directions describe not a single linear pathway but a positive feedback loop. An initial perturbation, whether a dysbiotic shift that admits the virus or a viral infection that depletes lactobacilli, sets in motion a cycle in which infection and dysbiosis each promote the other. Dysbiosis facilitates infection and impairs clearance, the infection, once established, suppresses the host peptides on which lactobacilli depend, deepening the dysbiosis and further compromising clearance. Such a self-reinforcing relationship would help to explain why infection and a non-lactobacillary microbiome are so consistently observed together in cross-sectional studies, why the severity of dysbiosis tends to parallel the severity of cervical disease, and why some infections persist while others, in women who retain a robust lactobacillary community, resolve spontaneously. This also has a therapeutic implication: if the relationship can be interrupted at the microbial level, for example by restoring lactobacillary dominance, the conditions that sustain viral persistence might be removed. The principal limitation of the current evidence is that the great majority of studies are cross-sectional and therefore cannot establish temporal sequence. Longitudinal investigations that pair serial microbiome characterization with repeated viral testing, ideally incorporating measures of viral integration and clearance, are required to confirm the existence and direction of this *relationship* and to determine at which point it is most amenable to intervention (Yang et al., 2022).

5. THERAPEUTIC PROSPECTS

If dysbiosis contributes to viral persistence, restoration of a lactobacilli-dominated community offers a rational therapeutic strategy. Probiotic supplementation, principally with *Lactobacillus species*, has been investigated for the restoration of vaginal eubiosis and the support of viral clearance. Verhoeven et al. (2013) reported, in a prospective controlled pilot study, that probiotic use enhanced the clearance of human papillomavirus-related cervical lesions, and Palma et al. (2018) described the long-term application of *L. rhamnosus* to restore a balanced vaginal ecosystem in the context of infection. Probiotics have also been shown to reduce the recurrence of bacterial vaginosis, the clinical correlate of dysbiosis (Mei & Li, 2022). A more recent and ambitious approach is vaginal microbiota transplantation, in which the entire microbial community from a healthy donor is transferred to a recipient with refractory dysbiosis, although still at an early, largely conceptual stage, it has been proposed as a means of achieving durable restoration of a protective community (Ma et al., 2019; Meng et al., 2024). These interventions remain preliminary, and robust randomised evidence of benefit for viral clearance is not yet available. Nevertheless, they represent a promising direction that follows logically from the observed microbiome-virus relationship.

6. IMPLICATIONS FOR SCREENING AND RISK STRATIFICATION

The consistent association between dysbiosis and infection raises the possibility of incorporating microbiome assessment into cervical screening. The clinical appeal of this prospect rests on the availability of targeted

molecular assays that quantify the dominant Lactobacillus and anaerobic groups and that can be performed on the same instruments already used for viral testing, without the cost and complexity of next-generation sequencing (Voroshilina et al.). Such assays could identify women whose dysbiotic microbiome places them at elevated risk of persistence, allowing more intensive follow-up, and could, in principle, identify candidates for microbiome-directed intervention. The evidence is not yet sufficient to justify the routine use of microbiome testing in screening, but its evaluation as an adjunct to existing methods is a reasonable and timely objective.

7. CONCLUSION

The vaginal microbiome is an important cofactor in the natural history of human papillomavirus infection. A lactobacilli-dominated community protects the lower genital tract, whereas dysbiosis is consistently associated with infection and, in many studies, with the severity of cervical lesions. The relationship is most plausibly bidirectional and self-reinforcing, with dysbiosis facilitating infection and the virus promoting dysbiosis. Restoration of a protective microbiome through probiotics or vaginal microbiota transplantation is a promising but as yet unproven therapeutic avenue, and microbiome assessment by targeted molecular assays merits evaluation as an adjunct within cervical screening. Longitudinal studies remain necessary to establish causation and to define the clinical utility of microbiome-based approaches.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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