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The role of the genital microbiota in the acquisition and pathogenesis of sexually transmitted infections

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Abstract

Purpose of review: There are an estimated 374 million new STI infections worldwide every year. Our review article examines the current evidence of how STI acquisition, transmission, and pathogenesis is impacted upon by the genital microbiota, with a focus on epidemiological, biochemical, and immunological features.

Recent findings: At least in women, a genital microbiota dominated by lactobacilli has long been considered optimal for reproductive health, while depletion of lactobacilli may lead to a genital microenvironment dominated by anaerobic pathogens, which can manifest clinically as bacterial vaginosis (BV). Recent research efforts have characterized genital microbiota composition in greater resolution, sometimes at species-level, using proteomics, metabolomics, and deep sequencing. This has enhanced our understanding of how specific microbiota members influence acquisition or clinical manifestation of STI pathogen infection. Other advances include a steady, though still slow, increase in the number of studies that sought to determine the genital (penile or urethral) microbiota of males and how it may impact that of their female partners' genital microbiota and risk of STI acquisition. Altogether, these data enabled us to explore the concept that genital microbiota may be sexually transmitted and influence pathogenesis and clinical presentation of other STI.

Summary:

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Conflicts of interest

The authors have no conflicts of interest.

With STI infection rates increasing worldwide, it is important now more than ever to find novel STI prevention strategies. Understanding if and how the genital microbiota is a modifiable risk factor for STI transmission, acquisition, and clinical manifestation may prove to be an important strategy in our efforts to curb morbidity in at risk populations.

Keywords

genital microbiota; dysbiosis; STI

Introduction

Global rates of sexually-transmitted infections (STIs) are on the rise[1], with significant burden of disease[2,3] and serious adverse outcomes, particularly in women, like pelvic inflammatory disease (PID) and obstetric consequences to both mother and baby when they occur during pregnancy (e.g., preterm birth reviewed in[4]). Women who have genital tract flora dominated by anaerobic bacteria and depleted in lactobacilli (cervicovaginal dysbiosis) are also at risk of PID and preterm labor [5,6,7**]. Microbe-induced inflammation in the context of either STIs or dysbiosis has been proposed as a possible mechanism of preterm birth[5,8]. Not only do STIs and BV share many epidemiological features in the at-risk communities, but they also overlap in time and space at mucosal surfaces[9,10,11]. It is possible that at the community level, their interplay may influence the acquisition and transmission of STI pathogens, while within hosts their interaction may influence pathogenesis and clinical manifestation of STIs. A deeper understanding of how STIs and genital microbiotas intersect may prove crucial in our quest to curb the morbidity of STIs and mitigate their reproductive and obstetric adverse outcomes.

The female genital microbiota has been extensively studied for more than a century, particularly with respect to the lower reproductive tract (vagina and ectocervix). The colonization of the upper genital tract, in the absence of pathogens, has been a controversial topic. The vaginal and ectocervical microbiotas share significant overlaps given their spatial proximity and contiguous luminal surface. Most data on the cervicovaginal microbiota have focused on bacterial flora. Fungi and other eukaryotes likely contribute to the genital flora, but remain largely understudied, though advances in sequencing technologies (e.g., metagenomics and better representation of fungal taxa in reference databases) are propelling this field forward. For our review, we have focused on bacterial cervicovaginal microbiotas.

Human male genital microbiota remains understudied (reviewed in[12,13]). A literature search of original articles in English using the terms “penile microbiota” or “male genital microbiota” or “urethral microbiota” returned only 20 relevant articles. Recently, there has been a concerted effort to accumulate more information about males[14,15,16,17]. Medical male circumcision alters the structure of the penile microbiota[15,17,18,19,20] and not surprisingly, the genital microbiota is likely shared between male and female sexual partners[21,22,23,24].

Finally, the pharynx and rectum are also important STI exposure sites. Each have characteristic microbial compositions and some mixing of rectal, pharyngeal and urogenital

microbes is likely[25]. Unlike the well-explored relationship between STIs and genital microbiota, only two published studies have investigated the rectal microbiota and pharyngeal microbiota associate with concurrent STI infections, specifically *Chlamydia trachomatis* and *Neisseria gonorrhoeae*[26,27].

The genital microbial landscape

Cervicovaginal microbiota composition can be assessed through various methods. For over 130 years, vaginal specimens from women have been evaluated with bacteriology and microscopy methods. In most women, these methods reveal a predominance of *Lactobacillus* species. Disruptions in lactobacilli-dominated vaginal flora have been considered a dysbiosis and are generally associated with increasing quantities of anaerobic bacterial species. Prior to the advent of sequencing technologies, Nugent scoring, a Gram stain microscopy approach, was one of the most systematic approaches in vaginal flora assessment. Nugent scoring distinguishes between large Gram-positive rods (consistent with *Lactobacillus*), small Gram-variable rods (consistent with *Gardnerella vaginalis*) and curved Gram-variable rods (consistent with *Mobiluncus spp.*)[28] and classify vaginal flora. A Nugent score 0–3 indicates abundant lactobacilli, Nugent score 4–6 indicates intermediate flora with presence of both lactobacilli and others, and a score 7–10 indicates few lactobacilli with high abundance of others (e.g., *G. vaginalis* and *Mobiluncus spp.).* As high throughput sequencing methods have been developed to assess the composition of microbial communities in a culture-independent fashion, the human vaginal microbial community has been characterized in unprecedented resolution. Sequencing-based molecular definitions of cervicovaginal microbiotas are now standard[13,29,30**,31**]. Reproductive aged women can be classified into five community state types (CSTs): CST I is dominated by *Lactobacillus crispatus*, CST II by *Lactobacillus gasseri*, CST III by *Lactobacillus iners*, and CST V with *Lactobacillus jensenii*. Low-*Lactobacillus* communities (CST IV) comprise of a variety of anaerobic bacteria. CST I-III are considered optimal, whereas CST IV reflects dysbiotic microbial communities[13]. Interestingly, women with *L. iners*-dominated vaginas can transition between *Lactobacillus* predominant and dysbiotic states[13,32].

Available evidence indicates that flora commonly detected in females also colonize the penis, including the distal urethra[15,16,17,18,19,33,34,35,36]. In uncircumcised males, the predominant taxa belong to *Prevotellaceae*, *Veillonellaceae*, *Clostridiales* family XI, *Actinomycetaceae*, *Coriobacteriaceae*, and *Porphyromonadaceae* families[18,19]; circumcision alters the structure of the penile microbiota in distinctive ways[15,17,18,19,20]. Reduction in total bacterial load and in prevalence of anaerobes (e.g., *Porphyromonas, Prevotella, Dialister, Mobiluncus, Fusobacterium)* in the coronal sulcus are observed following the procedure[18]. Interestingly, many of the bacteria with reduced prevalence after circumcision are organisms associated with female genital dysbiosis[15,17,18,19,20]. The notion that the male genital microbiota and female genital microbiota are interconnected between sexual partners is discussed further below (see “Sexual transmission of genital dysbiosis).

Bacterial Vaginosis (BV) and genital microbiota

Genital dysbiosis characterized by Nugent scores of 7–10 or by molecular typing as CST IV are associated with the development of vaginal symptoms, including vaginal discharge, pruritis, discomfort, and odor. Collectively, these clinical symptoms are now referred to as bacterial vaginosis (BV)[37**,38,39]. In the clinic, criteria known as Amsel criteria are often used to diagnose BV[40]. Molecular tests can also directly detect BV-associated bacteria with high specificity and sensitivity (summarized in[37**]), which can also be used to diagnose BV in patients with clinical syndromes consistent with BV. Microbiologically, BV is characterized by a depletion of lactobacilli other than *L. iners* and an increase in a diverse and heterogeneous group of anaerobic bacteria[41,42]. Low-*Lactobacillus* communities (CST IV), which comprise a variety of anaerobic bacteria, is a risk factor for having clinically diagnosed BV[43] and is termed molecular-BV[42]. BV is the most common cause of vaginal discharge globally with high disease and economic burden[39,44].

Symptoms associated with BV are thought to result from BV pathogenesis. The mechanism of BV pathogenesis is not completely understood, but recent work has begun to decipher some of its complex mechanisms (see this important review in same journal from 2020[45]). Underpinning our current understanding of BV pathogenesis are conceptual pathogenesis models put forward by Schwebke and colleagues[46,47]. An updated model was published in 2019[47]. In short, certain strains of *Gardnerella vaginalis* with high pathogenic potential, which may be sexually-transmitted[48,49], adhere to the epithelium and displace lactobacilli and instigate the formation of biofilm[50]. This is followed by an increase in *Prevotella bivia* abundance[51], which in synergy with *G. vaginalis* produces metabolites that facilitate their proliferation[52] and the degradation of the vaginal epithelium mucous layer, possibly through vaginal sialidases[53,54,55]. More recently, data have emerged for how *G. vaginalis* may be involved in epithelial cell layer integrity disruption[56]. Next, secondary colonizers are recruited to the biofilm, especially *Atopobium vaginae* that rarely co-occurs without *G. vaginalis*[57], possibly leading to the creation the polymicrobial biofilm characteristic of BV. This mature, resilient polymicrobial biofilm may explain why treatment for BV with classical antibiotics is not very effective[58]. Once the mature biofilm is established and the epithelial barrier is compromised, inflammation may ensue, possibly from a combination of secondary colonizers, since neither *G. vaginalis* and *P. bivia* induce a robust immune response[55,59]; exfoliating epithelial cells; and from recruited immune cells. By contrast, cervicovaginal secretions of women whose vaginas are dominated by *L. crispatus* have low levels of pro-inflammatory cytokines[60,61,62].

Metronidazole has been the standard treatment for BV with four-week cure rates approaching 85%. However, BV will recur in almost 60% of treated women within one year[58]. After BV treatment, women are likely to have their vaginal microbiota become dominated by *L. iners* suggesting that *L. iners*-dominant flora are at risk for loss of lactobacillus domination and progression of BV pathogenesis. Innovative treatment and prevention strategies are currently being explored, including the replenishment of *L. crispatus* following BV treatment via vaginal administration of live *L crispatus* strain CTV-05 (LACTIN-V[63,64**]. Though the use of LACTIN-V is experimental and not approved for treatment of any condition at this time, short-lived changes in vaginal flora

after LACTIN-V provides an important proof-of-principle that the vaginal microbiota may be modifiable. The use of vaginal probiotics comes with both pitfalls and hope for addressing the problem of recurrent BV[65,66].

Sexual transmission of genital dysbiosis

Evolving evidence suggests that this is a possibility both within heterosexual partnerships and among women that have sex with women (WSW)[21,22,23,24], though confounders exist: BV has been observed in sexually-experienced but self-reported abstinent women[67,68] and treating the male partners for BV has not improved female BV outcomes, though partner treatment studies had many limitations[69]. Specific microbes consistently identified in women with dysbiotic communities have also been associated with male urethritis[34]. Although vulvovaginal *Candida* is not considered sexually transmitted, male partners are more likely to be colonized with the same *Candida* strain[70,71]. Notably, the penile microbiome accurately predicts incidence of cervicovaginal dysbiosis in females who did not have it at baseline[72], suggesting the male niche may be a reservoir for microbes typical of female genital dysbiotic communities. Importantly, medical male circumcision offsets some of this risk[18] suggesting that anatomy (the foreskin) is likely the most important determinant of male genital microbial communities. Evidence in support of this hypothesis is summarized in Table 1.

Dysbiotic genital microbial communities are associated with sexually transmitted infections

Substantial published research shows that the composition of the cervicovaginal flora associates with STI risk. Flora dominated by *L. iners* or depleted in the other lactobacilli generally positively correlates with STIs, whereas flora dominated by non-iners lactobacilli negatively correlates with STIs. These findings come from numerous observational human studies, including longitudinal studies, some of which are prospective in design (Table 1). These observed associations have at least three possible explanations: i) non-lactobacillus dominant genital microbiota are simply a biomarker of host factors that promote susceptibility to STI pathogens or are promoted during the pathogenesis of STIs; ii) non-lactobacillus dominant genital microbiota could promote STI pathogenesis or symptomatology, therefore bringing asymptomatic STIs that might normally go unrecognized to clinical attention and therefore diagnosis; iii) non-lactobacillus dominant genital microbiota could promote acquisition of STI by impacts on host or directly on STI pathogens. We explore evidence for these possibilities below.

The cervicovaginal microbiota as a non-specific biomarker of STI susceptibility or STIs—Dysbiotic cervicovaginal microbiota in the absence of genital symptoms is common[85] and treatment of BV does not consistently lead to a reduced risk of STIs[86,87,88]. Studies that included BV treatment followed by a prospective follow-up for *N. gonorrhoeae*, *C. trachomatis* and *Mycoplasma genitalium* have shown mixed results[86,87,88]. Two of the three trials showed a reduced risk[86,87], while one trial of home screening and oral metronidazole did not[88], though differences in drug, route of administration, treatment duration and specimen collection must be noted. It is known that treatment of BV with metronidazole or other antibiotics reduces clinical symptoms but does not consistently

result in a change in genital microbiota to low risk, lactobacillus predominant flora. Despite a strong epidemiological link between HIV-1 acquisition and dysbiotic microbial communities, one longitudinal study of HIV-1/HSV co-infected women before and after antiretroviral therapy has shown that even when HIV viral load is suppressed the dysbiotic microbial communities persisted[89]. Similarly, despite strong observational evidence that the genital microbiota may influence HPV acquisition, recent studies have reported the opposite relationship, whereby HPV infections (albeit not all infections or genotypes) alter the vaginal microbiome by downregulation the secretion of host antimicrobial peptides at the genital mucosa via the production of HPV oncoproteins[90].

The genital microbiome influences STI symptoms and pathogenesis—The cervicovaginal microbiota may alter STI symptomatology, particularly the presence of vaginal discharge and discomfort, or in the case of HPV, viral persistence or development of pre-neoplastic lesions within the genital tract [91**](reviewed in[92]). These symptoms may bias towards STI test seeking behavior, at least for certain STI pathogens, since symptoms of localized inflammation in the genital tract are typical of both cervicovaginal dysbiosis (e.g., BV) and pathogens like *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium*, and *Trichomonas vaginalis*. These STI pathogens are all well known to also cause asymptomatic infection, especially in women[93,94,95], so it is possible that BV could prompt testing in individuals who might have had what would otherwise have been an unrecognized, asymptomatic infection.

Further, dysbiotic communities could potentiate the inflammatory response in the setting of another STI, precipitating symptoms and converting asymptomatic infections into recognized symptomatic infections. A small cross-sectional using sequencing examined the cervicovaginal microbial communities in women presenting with *N. gonorrhoeae* infection to a local STI clinic[96]. . The microbial composition was compared between women who presented to clinic reporting symptoms attributable to gonorrhea and those without symptoms[96]. Asymptomatic women had *L. iners*-dominant genital communities, while symptomatic women had diverse microbial communities without predominant lactobacilli. Vaginal microbiotas dominated by *L. crispatus* and/or *L. gasseri* have been associated with a decreased risk of HPV CIN3 progression[78,80] and persistence[79,81]. *Prevotella* has been implicated in persistence of high-risk HPV types and associated with higher expression of oncogenic and inflammatory markers[91**].

Genital microbiota influence STI acquisition—Several prospective studies of incident STIs and female genital microbiota (Table 2) indicate that genital communities influence STI acquisition risk. To our knowledge, *Treponema pallidum* has not been formally assessed in this context. By meta-analysis, microbiotas low in lactobacilli (by Nugent score, or sequencing, or inferred by Amsel criteria based BV diagnosis,) are associated with increased risk of HIV-1[97**,98,99], HPV[100**,101] and *C. trachomatis*[100**] by 1.5-fold and of *T. vaginalis* by almost 2-fold[102]. The evidence for *N. gonorrhoeae* and *M. genitalium* remains mixed[100**]. Only three studies exist that investigate how male genital microbiota associates with STIs and have focused on HIV-1 and HPV[16,21,35]. Studies of other STIs investigated the link between genital flora and STI risk indirectly by exploring protective effects of

medical male circumcision against syphilis, chlamydia, gonorrhea or trichomoniasis, with mixed results[79,103,104]. Partner studies, however, have shown that that uninfected male partners of women with BV are also more likely to be diagnosed with an HIV *vs.* controls [105] by three-fold, even when accounting for other known factors of HIV risk and irrespective of female viral load[106]. Other studies have indicated that the male genital microbiota is a significant risk factor for the female partner to be diagnosed with HSV-2, HIV, or BV[14,15,17,21,35] and medical male circumcision is associated with reduced risk of both BV and STIs in the female partner[33,79,80,81,82,83,84], further supporting the idea that dysbiotic genital flora is sexually transmitted.

There are mechanistic data to support the biological plausibility that the genital microbiota influences STI acquisition. The more the vaginal microbiota shifts towards dysbiosis and loss of non-iners lactobacilli, the more marked the genital inflammation[30**,107,108]. Elevated genital inflammation is an independent risk factor for HIV-1 acquisition[109,110]. Host inflammation likely ensues in genital dysbiosis in response to a compromised epithelial barrier and/or increased pH[111]. Upregulation of pro-inflammatory cytokines, which when present in measurable quantities in cervicovaginal fluid, is associated with an over 3-fold increased risk of HIV acquisition in women[109,112]. Pro-inflammatory cytokines remain low in HIV-1 exposed seronegative women[113]. A plausible mechanistic explanation is that a pro-inflammatory milieu is associated with increased levels of endocervical $CD4^+$ T cells[54,114,115], which facilitates local viral replication[116]. An inflamed vaginal microenvironment, as determined by quantification of pro-inflammatory cytokines, also lowered the efficacy of topical tenofovir to protect against HIV acquisition, even with high study participant adherence[117]. Further, specific microbes (*Gemella asaccharolytica*, *Sneathia spp*, *Prevotella bivia*, *Megasphaera* sp. type 2, *Mycoplasma hominis*, *Parvimonas spp. type 2, Prevotella timonensis)* have been found to directly affect HIV-1 acquisition[31**,97**,118], some in a dose dependent manner[118]. Further, *Prevotela timonensis*, a BV-associated bacterium previously shown to be associated with an increased risk of HIV-1 acquisition[31**,97**], subverts the protective role of Langerhans cells (LCs) to enhance HIV-1 uptake into LCs, which then deliver virus to HIV-1 target cells[119**]. Under typical conditions, LCs are protective because they destroy HIV-1 upon capture. Vaginal microbiotas dominated by *L. crispatus* and/or *L. gasseri* are associated with a decreased risk of HIV[69,73] and HPV[76,77,78,79,120]whereas vaginal microbiomes dominated by *L. iners* have been associated with increased risk of acquiring HIV[69,82,83] and *C. trachomatis*[84,85**]. It is likely that the acidic milieu, presence of glycogen, and an integral epithelial barrier of the *Lactobacillus*-rich environment are not conducive to pathogen colonization[9,10,11,121,122,123]. D-lactic acid produced by non-iners lactobacilli has been associated with in vitro growth inhibition of several bacteria[38,39] ,including *N. gonorrhoeae*[39]). The biofilm produced during BV pathogenesis may be a favorable landing spot for non-viral STI pathogens, akin to the opportunistic secondary bacterial colonizers of the BV biofilm.

Different explanations may apply to different STI pathogens. For example, both observational data and mechanistic data suggest that there is a high likelihood that the genital microbiota plays a key role in the acquisition of HIV-1, but its influence on HIV pathogenesis may be minimal, as there is no available evidence to show that the

genital microbiota is associated with progression to AIDS. In the case of HPV, the genital microbiota may influence pathogenesis (i.e., progression to CIN3 or persistence) or be a biomarker of HPV pathogenesis in a genotype-dependent manner, but it is unclear whether it increases risk of HPV acquisition. In the case of non-viral STIs, the microbiota likely plays dual roles in pathogenesis and acquisition, though this is difficult to disentangle because of limitations of prospective studies of non-viral STI studies conducted to date. These limitations include: asymptomatic screening has not always been part of the study design; genital microbiota has not always been evaluated before, during and after an STI infection (self-sampling strategies have recently been proposed to achieve higher sampling frequency because they are concordant to clinician-collected specimens[66]); finally, the number of available prospective studies, especially those that utilize molecular tools, varies among STIs, with *N. gonorrhoeae*, *M. genitalium* and *T. vaginalis* lagging behind HIV-1, HPV and *C. trachomatis*

Conclusions

STIs and the genital microbiota are interconnected both within individuals at the genital mucosa and within communities due to their overlapping epidemiologies. Multiomic approaches (genomics, proteomics, metabolomics) continue to expand our understanding of microbiota composition and function, especially when applied to prospective longitudinal studies in humans, since robust animal models are lacking. Both observational and mechanistic data exist to support that genital microbiota influences the acquisition and pathogenesis of STIs, but the exact nature of these relationships likely differ by STI pathogen. Overall, deciphering how STIs and the genital microbiota intersect would greatly benefit from prospective studies of acquisition with asymptomatic STI screening and molecular assessment of genital flora. Ideally, these studies would not be limited to females.

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Key points

- Epidemiological evidence suggests there is a strong correlation between prevalent and incident STIs pathogen detection (HIV-1, HPV, *C. trachomatis*, *T. vaginalis*, *N. gonorrhoeae*, *M. genitalium*) and the cervicovaginal microbiota. Mechanistic data support these correlation, though lack of appropriate animal models that recapitulate the complex human genital microenvironment has made this difficult to study. Evolving evidence suggests this correlation may also hold true for males as well, though this field is still nascent.
- It is plausible that different STI pathogens are influenced by the genital flora in different ways, either at the level of acquisition/transmission or pathogenesis.
- Genital dysbiosis is likely sexually transmitted

Table 1.

Evidence in support of sexual transmission of genital microbial dysbiosis

Key finding	References
Overlapping microbiota between concurrent heterosexual or lesbian partners, suggesting microbiota may be sexually exchanged	[14,33,73,74,75]
BV is not commonly observed among women who report no or minimal history of penile-vaginal intercourse	[76,77]
Sexual intercourse is a risk factor for BV and BV recurrence	[20,23,38,78]
Specific microbes consistently detected in females with BV also colonize the penis, including the distal urethra	[15,16,17,18,19,33,34,35,36]
Following medical male circumcision, there is a reduction of anaerobic bacteria among the penile microbiota, including BV-associated bacteria	[15,17,18,19,20]
Medical male circumcision is protective against BV in female partners	[33,79,80,81,82,83,84]
The penile microbiome accurately predicts BV incidence in Kenyan females who did not have BV at baseline and circumcision may offset some of this risk	[18,72]
Even though candidiasis is not considered an STI, male partners of females with vulvovaginal *Candida* albicans are more likely to be colonized with the same *C. albicans* strain	[70]
By meta-analysis, new and multiple concurrent male sexual partners increased the risk of BV by 1.6-fold (CI95%=1.5–1.8), while a history of female sexual partners increased the risk of BV by 2-fold (CI95%=1.7–2.3).	[38]
Protective role of condom use against BV and conversely inconsistent condom use increase BV risk	[20,38]

Table 2.

Longitudinal studies of prospective and retrospective design that evaluated the relationship between incident STIs and the female genital flora or bacterial vaginosis

Pathogen	Study design	Estimated effect of microbiota on STI acquisition	Timing and type (symptomatic/ asymptomatic) STI screening type	Method of microbiota assessment	Timing of microbiome assessment	Country of study	Study dates	Population	Sample size	Citation
HIV-1	**Prospective**	Prenatal aOR=3.7 (CI95 unclear Postnatal aRR=2.3 (CI95 unclear	Asymptomatic screening at first antenatal visit and at the postnatal 6-monthly visits	BV by Amsel clinical criteria	At first antenatal visit (late second trimester) and at the postnatal 6-monthly visits	Malawi	1990–1993	Pregnant and postpartum women at risk of HIV	2,365	[124]
	Prospective	HR=2.0 (CI95=1.2–3.5)	Monthly asymptomatic screening (median number if visits = 3)	Absence of lactobacilli by Nugent scoring	Monthly (concurrent with STI screening)	Kenya	1993–1997	Seronegative female sex workers	657	[125]
	Prospective	Nugent score 4–6): HR=1.54 (CI95=1.13–2.09) Nugent score 7–10: HR=1.86 (CI95= 1.40–2.47)	Monthly asymptomatic screening	Nugent scoring	Monthly screening. Syndromic management when clinically indicated	Kenya	1993–2012	High-risk seronegative women	1,954	[126]
	Prospective	Nugent score 4–6: aOR=2.01 (CI95=1.12–3.62)	Asymptomatic screening at first study visit and at the 6-monthly follow-up visit up to 36 months	BV by Amsel clinical criteria and flora by Nugent scoring	Monthly (concurrent with STI screening)	South Africa	2000–2002	Women screened for cervical cancer	410 (86 HIV seroconverters and 324 matched controls)	[127]
	Prospective	CST 4: HR=4.03 (CI95=1.14–14.27) CST 3: HR=4.22, (CI95=1.06–16.88)	Asymptomatic screening twice per week via fingerprick and HIV viral load testing every 3 months (median follow-up time of 336 days)	16S rRNA gene, region V4 sequencing	At the 3-monthly visits	South Africa	n/a	Young South African women (18–23 years) at risk of HIV acquisition in the FRESH (Females Rising through Education, Support and Health) study	236	[31**]
	Meta-analysis	Pooled RR=1.6 (CI95=1.2–2.1)	Repeated study-specific assessment	Nugent and Amsel's	Repeated study-specific assessment	Included 4 studies published before November 2005 from multiple populations		HIV-negative women prospectively measured for incident HIV infection	3,554	[97**]

Pathogen	Study design	Estimated effect of microbiota on STI acquisition	Timing and type (symptomatic/ asymptomatic) STI screening type	Method of microbiota assessment	Timing of microbiome assessment	Country of study	Study dates	Population	Sample size	Citation
HPV	**Prospective**	HR=0.99 (CI95=0.46–2.12)	Asymptomatic screening every 4 or 6 months	Amsel	At baseline, 12 months, and when women reported symptoms consistent with lower genital tract infections	USA	1990–2000	HPV-negative young women attending family planning clinics	105	[128]
	Prospective	Time lag analysis showed statistically significant temporal relationship between Amsel BV and HPV diagnosis, with HPV infection generally occurring first, or at the same time as BV. See original paper for effect sizes at different time lags.	Asymptomatic screening every 4 months for 3 years	Amsel	Concurrent with HPV screening	USA	1990–1997	Female university students	516	[129]
	Retrospective	adjRR=1.34 (CI95=1.11–1.63)	Asymptomatic screening at baseline and at 12 months	Nugent	At baseline and 12 months later (concurrent with hPV screening)	UK	2004–2007	Female university students	2075	[130]
	Prospective	IRR low-*Lactobacillus* flora=1.86 (CI95=0.52–6.74). See original paper for analyses of HPV remission rates which were slower in women with low lactobacillus communities.	Asymptomatic screening twice weekly for 16 weeks	16S rRNA gene, region V4 sequencing	Asymptomatic screening twice weekly for 16 weeks (concurrent with HPV screening)	USA	2005–2007	Women from general population and referral from gynecologic care	32	[131]
	Meta-analysis	Pooled RR among studies of incident HPV only = 1.33 (CI95=1.18–1.50)	Repeated study-specific assessment	Low-*Lactobacillus* microbiota states broadly defined by Nugent, Amsel's, Pap	Some but not all studies included had repeat microbiota evaluations (>2 measurements).	Included 14 studies published between 2003–2017. North American and European female populations. Longitudinal cohort (n=4) and case-control studies included (n=10)			5,281	[132**]

Pathogen	Study design	Estimated effect of microbiota on STI acquisition	Timing and type (symptomatic/ asymptomatic) STI screening type	Method of microbiota assessment	Timing of microbiome assessment	Country of study	Study dates	Population	Sample size	Citation
				smears or 16S rRNA sequencing						
	Meta-analysis	Pooled RR low-Lactobacillus microbiota among all included studies= 1.53 (CI95=1.23–1.82)	Repeated study-specific assessment	Microbiota dichotomized into low- and high-Lactobacillus by Nugent, Amsel's, or 16S rRNA sequencing	Some but not all studies included had repeat microbiota evaluations (>2 measurements).	Included 20 studies published between 2000–2016 of HIV-negative female populations. Incident and prevalent study designs included. PCR-based STI detection.			20,022	[100**]
C. trachomatis	Retrospective	HR=1.4 (CI95=0.9–2.3)	Monthly screening, irrespective of symptoms (median number of visits = 3)	Depletion of lactobacilli by Nugent scoring (Nugent score ≥4)	Monthly (concurrent with STI screening)	Kenya	1993–1997	Seronegative female sex workers	657	[125]
	Retrospective	aIRR=2.10 (CI95=1.10–3.80)	Monthly screening, irrespective of symptoms	Nugent	At baseline, every 6 months thereafter and when symtoms of genital infection were reported	Kenya	1998–2002	HIV-negative female sex workers	416	[133]
	Prospective	OR=0.7 (CI95=0.4–1.2) for women recruited from two of four the study sites OR=2.0 (CI95=0.8–4.7) for the women recurited from the other two of four study sites	Quaterly asymptomatic screening and symptomatic screening when clinically indicated	Nugent	Quarterly screening (concurrent with STI screening) (follow-up period unclear)	South Africa	2003–2004	Women from the general population	479	[134]
	Prospective	Nugent score of 7–10 and a score of 4–6 both conferred a 1–2-fold increased risk for incident chlamydial infection: Nugent score 4–6: aHR= 1.58 (CI95=1.20–2.08) Nugent score 7–10: aHR=1.75 (CI95=1.37–2.23)	Quarterly asymptomatic screening for 1 year	Nugent	Quarterly for 1 year (concurrent with STI screening)	USA	1999–2002	Women attending clinics for routine care	3,620	[135]

Pathogen	Study design	Estimated effect of microbiota on STI acquisition	Timing and type (symptomatic/ asymptomatic) STI screening type	Method of microbiota assessment	Timing of microbiome assessment	Country of study	Study dates	Population	Sample size	Citation
	Prospective	IRR=1.50 (CI95=0.70–3.40)	Asymptomatic screening at baseline, 6 months and 12 months follow-up visits	Nugent	At baseline, 6 months and 12 months follow-up visits (concurrent with STI screening)	Australia	2007–2008	Women attending primary-care, family planning and STI clinics	1,093	[136]
	Prospective	aRR=2.00 (CI95=1.10–3.90)	Asymptomatic screening at baseline	Nugent	At baseline and one follow-up visit concurrent with STI screening.	UK	2004–2007	Female University students	907	[137]
	Retrospective	aOR=1.34 (CI95=0.92–1.97)	Asymptomatic screening at enrollment, 6 months, and 12 months	Nugent	At enrollment and 3-monthly for 12 months	Tanzania	2008–2010	Women working in bars, hotels and recreational facilities (considered at risk for HIV)	956	[138]
	Prospective	aHR=1.45 (C95=0.91–2.30)	Quarterly screening irrespective of symptoms with a mean follow-up of 18 months	Amsel's	At enrollment	South Africa	2003 – 2005	Women from family planning, well-baby and general health clinics	435	[139]
	Meta-analysis	Pooled RR of low-Lactobcillus microbiota among all included studies=1.51 (CI95=1.22–1.81)	Asymptomatic screening	Microbiota dichotomized into low- and high-Lactobacillus by Nugent, Amsel's, or 16S rRNA sequencing	Some but not all studies included had repeat microbiota evaluations (>2 measurements).	Included 17 studies published between 2000–2016 of HIV-negative female populations. Incident and prevalent study designs included. PCR-based STI detection.			12,810	[100**]
Mycoplasma genitalium	**Prospective**	IRR=0.50 (CI95=0.10–3.40)	Asymptomatic screening at baseline, 6 months and 12 months follow-up visits	Nugent	Aat baseline, 6 months and 12 months follow-up visits (concurrent with STI screening)	Australia	2007–2008	Women attending primary-care, family planning and STI clinics	1,093	[136]
	Retrospective	RR=6.09 (CI95=1.98–18.50)	Asymptomatic screening at baseline and 12 months later	Nugent	At baseline and 12 months later (concurrent with hPV screening)	UK	2004–2007	Female University students	873	[140]
	Meta-analysis	Pooled RR of low-Lactobacillus microbiota among all included studies=0.49 (CI95=0.16–0.82)	Varies by study	Microbiota dichotomized into low- and high-Lactobacillus by Nugent scoring or	Some but not all studies included had repeat microbiota evaluations (>2 measurements)	Included 4 studies published between 2000–2016 of HIV-negative female populations. Incident and prevalent study designs included. PCR-based STI detection.			2,894	[100**]

Pathogen	Study design	Estimated effect of microbiota on STI acquisition	Timing and type (symptomatic/ asymptomatic) STI screening type	Method of microbiota assessment	Timing of microbiome assessment	Country of study	Study dates	Population	Sample size	Citation
				Amsel's criteria						
Neisseria gonorrhoeae	Retrospective	HR, 1.7; 95% CI, 1.1–2.6	Monthly screening, irrespective of symptoms (median number of visits = 3)	Absence of lactobacilli by Nugent scoring	Monthly (concurrent with STI screening)	Kenya	1993–1997	Female sex workers	657	[125]
	Retrospective	aIRR=0.8 (CI95=0.50–1.40)	Monthly screening, irrespective of symptoms	Nugent	At baseline, every 6 months thereafter and and when clinically indicated	Kenya	1998–2002	Female sex workers	416	[133]
	Prospective	OR=0.9 (CI95=0.5–1.24) for women recruited from two of four the study sites OR=0.9 (CI95=0.4–2.3) for the women recurited from the other two of four study sites	Quarterly screening for 12 months, irrespective of symptoms	Nugent	Quarterly screening (concurrent with STI screening)	South Africa; Tanzania; Zambia	2003–2004	Sexually-active women from the general population, including highrisk women	958	[134]
	Prospective	Nugent score of 7–10 and a score of 4–6 both conferred a 1–2-fold increased risk for incident gonococcal infection: Nugent score 4–6: aHR= 1.51 (CI95=1.00–2.28) Nugent score 7–10: aHR=1.43 (CI95=0.98–2.08)	Quarterly screening for 1 year, irrespective of symptoms	Nugent	Quarterly asymptomatic screening for 1 year (concurrent with STI screening)	USA	1999–2002	Women attending clinics for routine care	3,077	[135]
	Retrospective	aOR=1.44 (CI95–0.84–2.45)	Asymptomatic screening at enrollment, 6 months, and 12 months	Nugent	At enrollment and 3-monthly for 12 months	Tanzania	2008–2010	Women at hihg-risk of HIV	956	[138]
	Prospective	aHR=1.66 (CI95=0.83–3.32)	Quarterly screening irrespective of symptoms with a mean follow-up of 18 months	Amsel's	At enrollment	South Africa	2003 – 2005	Women from family planning, well-baby and general health clinics	435	[139]

Pathogen	Study design	Estimated effect of microbiota on STI acquisition	Timing and type (symptomatic/ asymptomatic) STI screening type	Method of microbiota assessment	Timing of microbiome assessment	Country of study	Study dates	Population	Sample size	Citation
	Meta-analysis	Pooled RR of low-Lactobacillus microbiota among all included studies=1.18 (CI95=0.88–1.47)	Varies by study.	Microbiota dichotomized into low- and high-Lactobacillus by Nugent scoring or Amsel's criteria	Some but not all studies included had repeat microbiota evaluations (>2 measurements).	Included 8 studies published between 2000–2016 of HIV-negative female populations. Incident and prevalent study designs included. PCR-based STI detection.			8,799	[100**]
Trichomonas vaginalis	Prospective	Nugent score 4–6: aHR= 1.39 (CI95=1.00–1.92) Nugent score 7–10: aHR=1.495 (CI95=1.48–2.57)	Quarterly asymptomatic screening for 1 year	Nugent scoring	Quarterly asymptomatic screening for 1 year (concurrent with STI screening)	USA	1999–2002	Women attending clinics for routine care	3,077	[135]
	Prospective	aHR=1.60 (CI95=1.00–2.57)	Quarterly screening irrespective of symptoms with a mean follow-up of 18 months	BV by Amsel's criteria	At baseline	South Africa	2003 – 2005	Women from family planning, well-baby and general health clinics	435	[139]
	Prospective	BV at the same visit as *T. vaginalis* detection: aOR=1.90 (CI95=1.16–3.09)	Monthly screening, irrespective of symptoms (folow-up duration unclear)	Nugent scoring	Monthly screening (concurrent with *T. vaginalis* screening).	Kenya	2003–2005	HIV seronegative and seropositive sex workers	570	[141]
	Retrospective	Nugent score 4–6 at previous visit: aHR= 1.73 (CI95=1.21–2.19 BV at previous visit: aHR=2.40 (CI95=1.92–3.00)	Quarterly visits up to 30 months	Nugent scoring	Quarterly visits up to 30 months	Malawi; South Africa; USA; Zambia; Zimbabwe	1993–2005	HIV-negative, not pregnant, sexually active women	2,920	[142]
	Retrospective	Nugent score 4–6: aIRR=0.46 (CI95=0.20–1.09) BV (Nugent score 7–10): aIRR=1.13 (CI95=0.74–1.72)	Every 10 months for 3.5 years, irrespective of symptoms	Nugent scoring	At baseline	Uganda	2005–2008	Sexually active women	2,374	
	Retrospective	Nugent score 4–6: aHR= 1.39 (CI95=1.00–1.92) Nugent score 7–10: aHR=1.50 (CI95=1.48–2.57)	Quarterly screening for 1 year, irrespective of symptoms	Nugent scoring	Quarterly asymptomatic screening for 1 year (concurrent with STI screening)	United States	1999–2002	Women attending clinics for routine care	3,077	[135]

Pathogen	Study design	Estimated effect of microbiota on STI acquisition	Timing and type (symptomatic/ asymptomatic) STI screening type	Method of microbiota assessment	Timing of microbiome assessment	Country of study	Study dates	Population	Sample size	Citation
	Retrospective	*T. vaginalis* incidence postively correlated with presence of several BV anaerobes. See original paper for effect sizes.	Monthly, irrespective of symptoms	Nugent scoring and ttaxon-specific quantitative PCR of the 16S ribosomal RNA gene	Monthly	Kenya	1999–2004	HIV-negative, not pregnant	68	[143]
	Prospective	OR=2.7 (CI95=2.1–3.5)	Quarterly screening, irrespective of symptoms, and when clinically indicated for 12 months	BV by Nugent scoring	Quarterly screening (concurrent with STI screening) (follow-up period unclear)	South Africa; Tanzania; Zambia	2003–2004	Sexually active women from the general population, including highrisk women	958	[134]
	Retrospective	IRR=8.0 (CI9= 3.2–19.8)	Monthly screening, irrespective of symptoms	Bv by Nugent scoring	At baseline, every 6 months thereafter and and when clinically indicated	Kenya	2003–2004	HIV-negative sex workers	466	[133]
	Retrospective	OR=1.9 (CI95=1.6–2.3)	Every 3 months for 12 months	Bv by Nugent scoring	Every 3 months for 12 months	United States	1998–2002	Not pregnant	3,620	[144]
	Retrospective	HR=1.8 (CI95=1.3–2.4)	Monthly screening, irrespective of symptoms (median number of visits = 3)	Absence of lactobacilli by Nugent scoring	Monthly (concurrent with STI screening)	Kenya	1999–2003	HIV-negative sex workers	657	[125]
	Retrospective	Nugent score 4–6: aOR=1.87 (CI95=1.39–2.52) Nugent score 7–10: 1.73 (CI95=1.36–2.20	Every 6 months for up to 7 years, irrespective of symptoms	Nugent scoring	Every 6 months for up to 7 years	United States	1993–1997	High-risk women	1,310	[145]
	Retrospective	aRR=9.0 (CI95=4.05–20.02)	At baseline, 3 months and 6 months, irrespective of symptoms	Nugent scoring	At baseline, 3 months and 6 months, irrespective of symptoms	India	1993–1995	Not pregnant, sexually active	853	[146]
	Meta-analysis	Pooled aHR=2.08 (CI95=1.69–2.56) and pooled aOR=1.87 (CI95=1.45–2.40)	Differed by study (symptomatic and asymptomatic screening).	BV defined by Amsel's criteria or a Nugent score of 7–10.	Only studies in which BV and *T. vaginalis* were assessed at the same timepoint and incident *T. vaginalis* was also assessed	Included 12 observational studies of incident trichomoniasis among women of any age.			18,424	[102]

Pathogen	Study design	Estimated effect of microbiota on STI acquisition	Timing and type (symptomatic/ asymptomatic) STI screening type	Method of microbiota assessment	Timing of microbiome assessment	Country of study	Study dates	Population	Sample size	Citation
					at a subsequent timepoint					

A=adjusted; OR=odds ratio; HR=hazard ratio; RR=risk ratio; IRR=incidence rate ratio; CI95= 95% confidence intervals; BV=bacterial vaginosis; CST=community state type by sequencing