Resource landscape shapes the composition and stability of the human vaginal microbiota

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The vaginal microbiota has demonstrated associations with women's and newborns' health. Despite its comparatively simple composition relative to other human microbiota systems, the ecological processes that underpin the dynamics and stability of vaginal microbial communities remain mechanistically elusive. A crucial, yet so far underexplored, aspect of vaginal microbiota ecology is the role played by nutritional resources. Glycogen and its derivatives, produced by vaginal epithelia, are accessible to all bacterial constituents of the microbiota. Concurrently, free sialic acid and fucose offer supplementary nutritional resources for bacterial strains capable of cleaving them from glycans, which are structurally integral to mucus. Notably, bacteria adept at sialic acid exploitation are often correlated with adverse clinical outcomes and are frequently implicated in bacterial vaginosis (BV). In this study, we introduce a novel mathematical model tailored to human vaginal microbiota dynamics to explore the interactions between bacteria and their respective nutritional landscapes. Our resource-based model examines the impact of the relative availability of glycogen derivatives (accessible to all bacterial species) and sialic acid (exclusive to some BV-associated bacteria) on the composition of the vaginal microbiota. Our findings elucidate that the prevalence of BV-associated bacteria is intricately linked to their exclusive access to specific nutritional resources. This private access fortifies communities dominated by BV-associated bacteria, rendering them resilient to compositional transitions. We provide empirical support for our model's predictions from longitudinal microbiota composition and metabolomic data, collected from a North American cohort. The insights gleaned from this study shed light on potential pathways for BV prevention.

Vaginal microbiota | *Lactobacillus* | *Gardnerella* | women's health | community ecology | metabolomics

The integration of community ecology theory in human microbiota studies remains a central goal, as ecological processes that shape microbial community composition hold the key to understanding the role of microbiota in health and disease (1). Gut microbiota garners most of the attention among human microbiota systems. Nevertheless, the application of traditional ecological theories to the intestinal milieu lags behind the exhaustive descriptions and experimental approaches, because of the diversity of these communities, which display between-individual variability, temporal composition fluctuations, as well as within-host spatial diversity in different regions of the digestive tract. As such, the classification, and even the existence itself, of distinct microbiota community types in the gut (known as 'enterotypes') remains contentious (2). Yet, establishing clear definitions of microbial community types remains a pivotal tool for understanding and predicting dysbiosis, understood here as imbalances or deviations from eubiotic and optimal states (3). While a complete mechanistic understanding of the roles of human microbiota in the host's physiology remains out of reach, a promising avenue focuses on applying ecological theory to the dynamics in chemostat bioreactors, in which defined bacterial communities are cultured under controlled settings (4–7). Under such *in vitro*, simplified conditions, mathematical ecological can describe interactions between bacteria and their environment to uncover factors shaping the composition of these synthetic microbial communities. Nonetheless, the extent to which these findings from *in vitro* settings scale up to *in vivo* microbial communities and, more generally, how ecological theory can improve our understanding of microbiota dynamics remains an open question. In this work, we use mechanistic modelling of the vaginal microbiota to shed light on the observed community composition dynamics and inform therapeutic options for treating vaginal dysbioses.

Compared to other human microbiota systems, the relative simplicity of the composition of vaginal microbial communities is ideal for applying ecological theories. Unlike enterotypes of the intestinal microbiota, the existence and definition of vaginal community state types, or CSTs are widely used, and have been well-documented in association with health or disease outcomes (8, 9). Briefly, the human vaginal microenvironment is most often dominated by one of four species of *Lactobacillus* (8, 10): CST I, dominated by *L. crispatus*; CST II, dominated by *L. gasseri*; CST III, dominated by *L. iners*; and CST V, dominated by *L. jensenii*. These CSTs are considered "optimal" meaning that they minimise the risk of disease and adverse effects, even though the optimality of CST III remains debated (11). In contrast, in CST IV, lactobacilli are not the most prevalent bacteria, and the microbiota is constituted instead of a diverse array of strict and facultative anaerobes. Such a composition of the vaginal microbiota is consistently associated with adverse gynecological, obstetric, and mental health outcomes, including sexually transmitted infections (12) and *in vitro* fertilisation procedure failure (13), and, therefore, often considered as 'non-optimal'. Bacterial vaginosis (BV), a condition characterized by symptoms such as vaginal odour and discharge and associated with severe discomfort (14), is experienced by approximately 23 to 29% of women of reproductive age, depending on the region (15).

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Microbiologically, the vaginal microbiota in women suffering from BV systematically corresponds to CST IV, although the reverse is not necessarily true as many women with this CST do not exhibit any symptoms (13) and there are other CST IV-associated conditions than BV (12). Despite the relative tractability and well-established health implications of the vaginal microbiota, the application of ecological theory to understanding this dynamic system remains limited.

Here, we develop a mathematical model of the vaginal microbiota and the associated nutritional resource landscape. We examine how the relative availability of, on the one hand, glycogen (a resource shared among all bacteria) and its derivatives such as glucose, maltose, and maltotriose, and, on the other hand, sialic acids and fucoses (the ability to release sialic acid from mucin-associated glycans is unique to some BV-associated bacteria), affects the vaginal microbiota composition. We show that the relative frequency of BV-associated bacteria hinges upon the relative supply of resources private to them (sialic acid and fucose from the mucus), and that the access to private resources makes communities dominated by BV-associated bacteria resistant to transition. By leveraging vaginal microbiota compositional and metabolomic data longitudinally collected from a cohort in North America, we provide compelling evidence that corroborates the predictions of our model. These findings have implications for BV prevention and provide indications for targeted interventions to improve women's sexual and reproductive health.

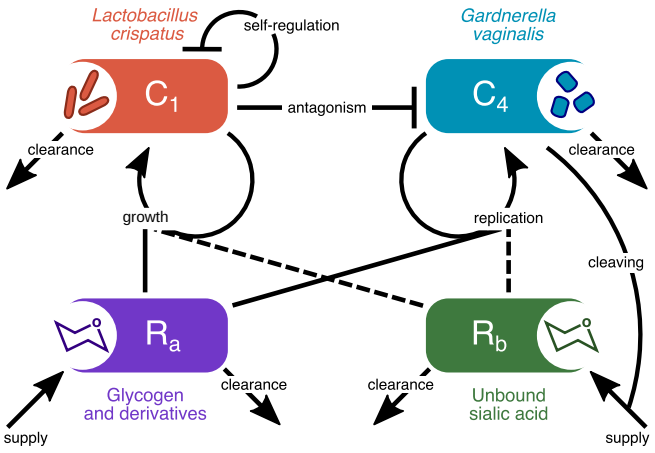

Fig. 1. Diagram of the consumer-resource vaginal microbiota model. We track the dynamics of two vaginal microbiota types (CST I and CST IV associated bacteria; C_1 and C_4) and the primary (R_a) and secondary resource (R_b) utilised by the two communities. The arrows among compartments represent density-dependent interactions including resource-mediated bacterial growth; lactic-acid-mediated density regulation (self-regulation and antagonism); resource supply; sialic acid cleaving; and background clearance of bacteria and resources. The dashed arrow indicates limited cross-feeding on the secondary resource. The representative species and, or molecules for each model component are listed. The corresponding mathematical model based on ordinary differential equations is detailed in the Methods section.

Modelling vaginal microbiota ecology

Mathematical models are instrumental in community ecology to study the consequences of non-linear interplay between species. A large body of theoretical exploration of microbiota systems has relied on classic competitive Lotka-Volterra models, often focusing on species interactions, while overlooking resource availability and consumption as a key driver of bacterial growth and population size (16–18). In contrast, the work described here builds upon classic models of consumer-resource theory (19, 20), which assumes resources to be the primary drivers of community composition and assemblage.

We adopt a parsimonious approach in modelling the composition of the vaginal microbiota and focus on two communities associated with distinct health manifestations (Fig. 1): on the one hand, a CST I vaginal microbiota, dominated by *L. crispatus*, that maintains an acidic vaginal micro-environment and in which BV-associated bacteria tend to perform poorly; on the other hand, a CST IV vaginal microbiota consisting of an assemblage of strict and facultative anaerobic bacteria, typically including species within *Gardnerella*, *Prevotella*, and *Fannyhessea* genera. Both CST II and CST V (dominated by *L. gasseri* and *L. jensenii*, respectively) are less prevalent and generally considered functionally analogous to CST I (21). As mentioned above, the association of CST III (dominated by *L. iners*) with a clinical presentation remains debatable and does not feature in our model as a distinct entity. Herein, we use the CST identity to refer to its typical microbial profile and implication on health outcomes: *i.e.*, CST I is characterised by a high prevalence of lactobacilli and is compatible with optimal vaginal physiology, while CST IV is characterised by the presence of strict and facultative anaerobes and is most often associated to specific clinical presentations (21).

In our work, we track the availability of two types of nutritional resources (Fig. 1): first, glycogen and its derivatives, which constitute a universal energy source for all vaginal microbiota bacterial components (22), and, second, sialic acid and fucose molecules, which are available as sialogycans attached to mucins that form mucus. Some common anaerobes can access these resources through the production of sialidases and fucosidases respectively, while *L. crispatus* is unable to leverage these resources for growth (23). The majority of *L. crispatus* strains cannot metabolise sialic acid. Furthermore, the strata formed by the sialic acid-cleaving bacteria (with potential biofilms) allows them to secure private access to this resource, as well as to the associated glycans.

Finally, we modelled the inhibitory interactions mediated by lactic acid produced by lactobacilli (Fig. 1). Acidity contributes greatly to the ecology in the vaginal environment by differentially affecting bacterial activity. Bacteria commonly found in CST IV vaginal microbiota often require a vaginal pH > 4.5 to grow and are growth restricted at a lower pH (8, 24) while lactobacilli have a higher tolerance to acidic conditions but show some growth inhibition at lower pH (< 4.0) (24, 25). We note that CST I antagonism towards CST IV in our model represents the net effect of all antagonism mechanisms, including lactic acid and other molecules produced by lactobacilli, such as bacteriocins, as well as the counter-adaptation processes that CST IV bacteria use (e.g., the production of biogenic amines) (21, 26).

Changes in the composition and activity of vaginal microbiota can occur in rapid succession in the vaginal environment, including daily fluctuations (27). Therefore, the model assumes that the resources and bacterial activity reach equilibrium rapidly and our analysis focuses on steady-state conditions. Our model is based on a system of ordinary differential equations (ODEs). Its formulation and the mathematical analyses are described in Methods.

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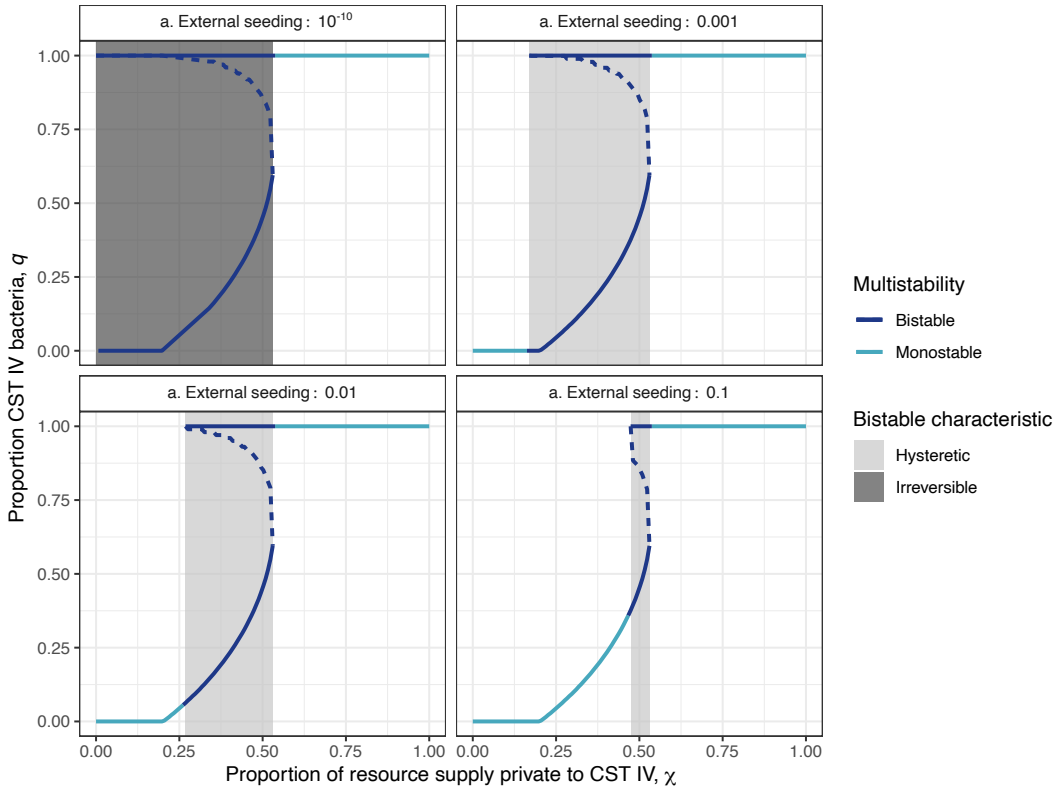

Fig. 2. Vaginal microbiota communities undergo a hysteretic or even irreversible transition to CST IV dominance as the proportion of resource supply private to CST IV increases. Solid lines indicate stable steady states with light blue and dark blue indicating monostable and bistable states, respectively. The dashed lines indicate the separatrix which separates two basins of attraction, each with a stable state. The propensity to recover from CST IV dominance (i.e., the left edges of the light grey window) depends on the minimum initial proportion of CST IV bacteria, which we interpret as the external seeding of vaginal bacteria. In the absence of sufficient external seeding (e.g., the 10^{-10} bacteria per unit of time panel), the CST dominance is irreversible. The region of bistability decreases as the external bacterial seeding increases.

Insights from mathematical modelling

We find that the resource landscape in the vaginal microenvironment can shape the composition and structure of the vaginal microbiota. Broadly, our numerical analysis demonstrates that an initially CST I-dominated vaginal microbiota undergoes a transition to CST IV as the proportion of resource supply that is private to CST IV bacteria increases (Fig. 2). When only a small fraction of resources is accessible privately to CST IV, CST I dominates the system since compounds like lactic acid directly inhibit bacteria associated with CST IV. When more private resources are supplied to CST IV, it gains dominance, as the benefits from the additional resources eventually outweigh the disadvantages caused by direct suppression from lactobacilli. We observe a plurality of both CSTs under the same resource condition (Fig. 2; grey shading). Such pluralities in our system are maintained through a combination of bistability (where either state, i.e., of single species-dominance, is stable, depending on the initial state of the system) and the stable coexistence of multiple species.

We find that the propensity to convert a CST IV to a CST I vaginal microbiota is influenced by the extent of external microbial seeding of CST I. Importation of external microbes to the vaginal milieu may take place through sexual intercourse, contamination from other body parts, and lactobacilli-based probiotics (28–30). In our model, if the external seeding of CST I bacteria is insufficient, the CST IV dominance becomes irreversible (Fig. 2a). This finding is consistent with our assumption of a closed system, wherein any increase in the bacterial populations is assumed to be generated solely by bacterial growth, precluding CST I from increasing in frequency if they are initially absent. However, a small initial seeding of CST I (e.g., at least 0.1% of the total initial frequency is made up of CST I despite CST IV dominance) is enough to cross over an unstable equilibrium (i.e., separatrix) and escape the basin of attraction associated with CST IV dominance as long as the resource landscape allows for CST I existence (i.e., sufficiently low χ; Fig. 2 b–d).

With an open system, transitions to CST IV become hysteretic, meaning that recovery from CST IV requires a larger reduction in the CST IV private resources (e.g., sialic acid and fucose) than the initial increase that triggered a transition from CST I to IV. While it is challenging to demonstrate hysteresis in natural settings, hysteretic shifts along a resource gradient have been recently demonstrated in chemostats of intestinal microbes (7). As the external seeding increases, we find that the window of bistability and hence hysteresis shrinks (Fig. 2; grey shading), supporting that external seeding of CST I (i.e., lactobacilli-based probiotics) may represent a promising strategy to restore the lactobacilli-rich community.

Corroborating theory with clinical data

To validate theoretical insights, we leverage human vaginal microbiota and metabolomics data to corroborate our prediction that the relative supply of resources private to CST IV (i.e., χ) is a key driver of compositional dynamics in the vaginal microbiota. A key challenge in examining mechanistic model predictions with empirical data is that ecological processes of interest are often difficult or impossible to measure directly. For instance, it is not possible to directly observe the absolute or relative quantities of incoming resources (i.e., rates of glycogen and sialic acid supply). Yet, the measured quantity of resource-associated metabolites, such as sialic acid and glycogen derivatives (e.g., glucose, maltose, and maltotriose) can provide valuable information when combined with a mechanis-

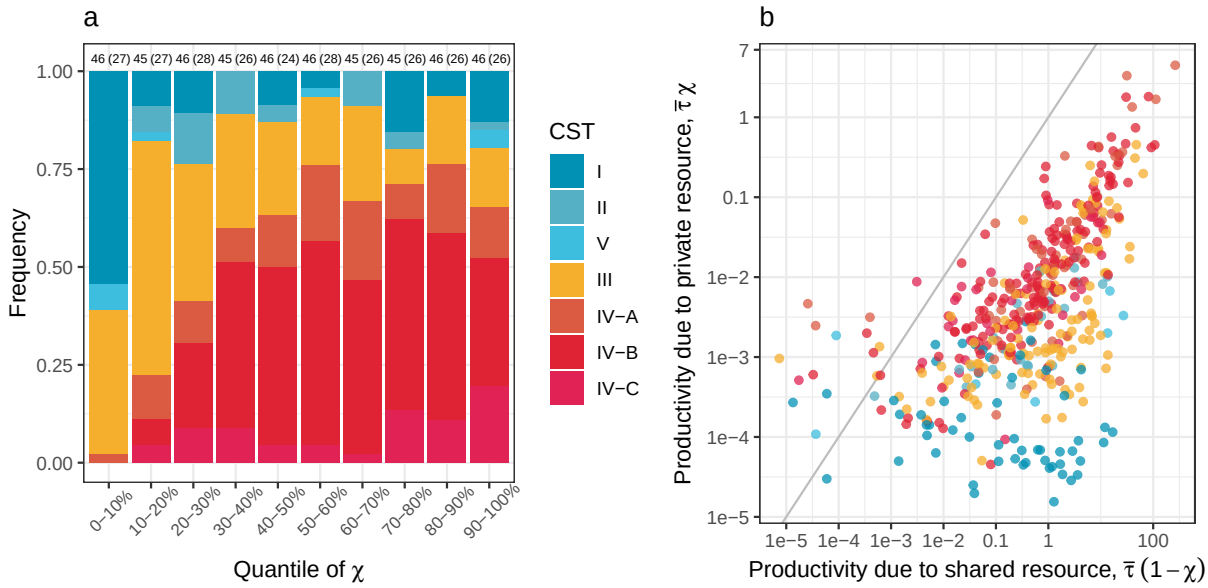

Fig. 3. Microbiota and metabolomics data support our model prediction that resource availability shapes human vaginal microbiota structure. a) Higher supplies of private resources more frequently support CST IV-dominated communities. Shown are the frequencies of CSTs as a function of quantiles of empirically estimated χ, the proportion of supplied resource private to CST IV (i.e., sialic acid). The numbers on top of each bar indicate the numbers of samples (and women in parentheses), respectively. b) Both the relative, and absolute resource supply quantity affect vaginal microbiota compositions. Shown are CST classification as a function of the productivity due to shared (x-axis) and private resources (y-axis). The grey diagonal line indicates an equal supply of the two resource types. Sensitivity analyses of these results to different model assumptions are provided in Supplementary Text S3.

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tic ecological model. On their own, these metabolites may be misleading as proxies for resource supply because they are influenced by distinct ecological processes including the resource supply rate, resource processing (e.g., sialic acid and fucose cleavage by CST IV bacteria), and consumption. Our model addresses this issue by delineating these processes explicitly, enabling us to derive an expression for resource supply that is independent of resource consumption by bacteria (equation 8 in Extended Methods S1). By incorporating these expressions with *in vivo* data on resource-associated metabolites and microbiota composition, we estimated the extent of shared (i.e., glucose, maltose, and maltotriose) and private (i.e., sialic acid) resource supply for each clinical sample.

Analysis of data from this cohort corroborate that the composition of human vaginal microbiota is associated with variations in resource supply: an increased relative supply of private resources (χ) is associated with increased colonization by CST IV bacteria (Fig. 3a). In particular, at the lowest 10% quantile of the relative private resource supply, *L. crispatus*-dominated CST I was the most common type (25 out of 46 samples) while the occurrence of CST IV was very rare (1 out of 46 samples). Beyond the 30% quantile, the CST IV frequency consistently exceeded 50% (Fig. 3a). Our findings were qualitatively identical across a wide range of model assumptions, with the exception of a scenario in which private resources are virtually inaccessible due to sialidase inactivity (Supplementary Text S3).

While the resource-ratio theory focuses on the relative supply of resources, empirical ecological studies have also highlighted the importance of considering the absolute resource supply as a driving factor in community dynamics (31). Examining the *in vivo* data closer, the absolute, rather than relative, supply appears to be a stronger determinant of bacterial composition at the upper and lower extremes of sialic acid supply (Fig. 3b): CST I and its functional analogues II and V are rarely found at high sialic acid supply (beyond $\overline{\tau}\ \chi = 10^{-2}$) while CST IV is rarely found at low sialic acid supply (below $\overline{\tau}\ \chi = 10^{-4}$). At intermediate sialic acid supply levels, increasing the supply of glycogen derivatives is associated with a reduction in CST IV, most notably in favour of *L. iners*-dominated CST III, which has been hypothesised to act as a functional gateway between CST I and CST IV (21).

Discussion

Community ecology has long been proposed to be a useful framework to understand human microbiota dynamics. Our theoretical and empirical results provide compelling evidence that resource ecology is a key factor shaping the composition and structure of the vaginal microbiota. While previous studies have demonstrated that elevated glycogen levels favour lactobacilli (32) and that sialidase activity affords *G. vaginalis* access to resources not accessible to lactobacilli (33), our findings bring into focus the importance of the balance between these two resource types. Specifically, we demonstrate that CST IV vaginal microbiota depend upon the relative, and to some extent, the absolute abundance of resources private to those communities.

Supplementing private resources to help beneficial microbiota has been proposed in the context of improving gut microbiota health (34). Unfortunately, it is not clear if there are private resources for lactobacilli in the vaginal milieu. A recent study shows that these bacteria can hydrolyse innate immune peptides into free amino and metabolise them for their growth (35). However, the relative importance of this additional source and the extent to which CST IV-associated bacteria engage in similar metabolic feats remain an open question. A search

for lactobacilli-private resources warrants further inquiry as our model demonstrates that private resource availability is a major force shaping the vaginal microbiota.

Mechanistic ecological modelling of vaginal microbiota is in its infancy (18, 36). Thus, there are ample opportunities for the future development of system-specific details. For example, one could explicitly model *L. iners* (CST III), whose unique features (i.e., a small genome size and carries a cytotoxin, inerolysin) and role as a transitional, or gateway taxon between CST I and IV has been increasingly recognised in recent years (11). Even within CST I and IV, there are known differences between lineages. For example, some L crispatus strains can metabolise sialic acid, when most cannot. Therefore, incorporating within-CST diversity into our model could yield as interesting results as increasing the number of CSTs.

Ecological details of the vaginal milieu are often tentatively known and variability among women and vaginal microbiota is rarely characterised quantitatively. Yet, our local sensitivity analyses (Supplementary Text S2) demonstrate that details of within-host ecology — including resource supply and acquisition, relative growth rates, and competition as well as external microbial input — play a key role in shaping the structure of the human vaginal microbiota. Specifically, the factors identified to promote CST IV communities included: low productivity of the vaginal microbiota, sialidase activity efficiency, high CST IV-associated bacteria growth rate, low lactic acid production (slow acidification affords increased competition for resources), low antagonism from CST I (Supplementary Text S2). Fully parameterised with relevant data, mechanistic models can generate quantitative predictions of the vaginal ecological interactions. Additionally, these models can facilitate *in silico* experiments that explore the consequences of interventions and counterfactual scenarios. To gain a systematic understanding of the ecological diversity of the vaginal microenvironment, the recent development of biomimetic *in vitro* models of vaginal epithelium offer a promising avenue (37). Biomimetic *in vitro* models enable the cultivation and manipulation of reconstructed vaginal microbiota sourced from biological samples, providing a high-throughput approach for cataloging the diversity of vaginal microbiota across different contexts.

A key advantage of the development of a mathematical model is to shed light on knowledge gaps in the literature which future empirical studies may address. For example, the two resource types in our model are assumed perfectly substitutable, i.e., offer equal value to growth. Given that glycogen — a shared universal resource — is freely available in the extracellular milieu while sialic acid molecules — private resource only accessible to CST IV-associated bacteria — require activity by sialidases that cleave sialic acid from sialoglycans associated with mucins with potential handling time by the bacteria, it is conceivable that glycogen-fueled growth may be more energy efficient for CST IV-associated bacteria. Here again, *in vitro* experiments can test differential CST IV-associated bacteria growth under varied nutritional combinations and identify optimal nutritional requirements. Such positive feedback between mathematical model development and experiments will enable the future development of model-assisted prognostic tools and novel rationally designed treatment options.

Supporting Information (SI). Extended methods and Supplementary Results.

Materials and Methods

Mechanistic ecological model of vaginal microbiota. At the fundamental level, our model can be interpreted as a consumer-resource model (38) in which n communities of consumers (C_i, here bacteria) and their resource (R) are described by a set of ordinary differential equations:

$$\frac{\mathrm{d}C_i}{\mathrm{d}t} = -\gamma_C\ C_i + \lambda_i \frac{R}{\kappa + R} C_i - \alpha_{j,i}\ C_j\ C_i \qquad [1a]$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \eta_R - \gamma_R\ R - \sum_{i=1}^{n} \lambda_i \frac{R}{\epsilon(\kappa + R)}\ C_i \qquad [1b]$$

where the growth of consumer type i is determined by the maximum intrinsic growth rate (λ_i), conditioned upon the availability of the resource (R) following a Monod (or Holling type II) function ($R \mapsto \frac{R}{\kappa+R}$ where κ represents the half-saturation constant, i.e., resource needed to achieve half the maximum growth). The resource is supplied to the system at a constant rate (η_R) and the resource and consumers exit the system at a background rate of γ_R and γ_C, respectively. The resource is consumed by C_i at a rate $\lambda_i \frac{R}{\epsilon(\kappa+R)}$ where ϵ corresponds to the yield (i.e., units of resource consumed per bacterial growth). Unlike classic consumer-resource models (e.g., (20)), we consider inhibitory interactions with $\alpha_{j,i}$ indicating the impact of type j on i, *i.e.*, a microbial Lotka-Voletera model with indirect interactions (39). Our work develops this generic model (eq. 1) focusing on two aspects of vaginal microbiota that functionally distinguish CST I from CST IV, namely differential resource use and lactic acid production with its inhibitory effect on bacterial populations.

a) *Differential resource use.* The human vagina is lined with stratified layers of epithelial cells, which are renewed and shed from the basal and outer layers, respectively. Epithelial cells store carbohydrates in the form of glycogen, which may be released to the extracellular milieu by shedding outer epithelial cells and through the destruction of immature cells (i.e., cytolysis) by *G. vaginalis* and other CST IV species (21). The degree to which each mechanism contributes to the availability of extracellular glycogen is unclear. However, the strong negative association observed between pH and cell-free glycogen suggests that glycogen release is driven predominantly by a CST IV independent mechanism (32): as *G. vaginalis* dominance is associated with elevated pH, one would expect a positive association if cytolysis was a key driver. Once released by shedding outer epithelial cells, glycogen and its breakdown derivatives (*e.g.*, glucose, maltose, maltotriose, maltopentaose, maltodextrins) constitute the primary fuel for vaginal bacterial growth, and they are utilised by both CST I and IV bacteria (22, 40). In addition to glycogen, CST IV bacteria are capable of metabolising additional resources. Specifically, *G. vaginalis* can cleave off sialic acid and fucose molecules from large sugar molecules that comprise the vaginal mucus layer (i.e., mucus sialoglycan) (23, 33). As the CST I does not appear to metabolise the end products of mucus degradation (23), we can consider sialic acid and fucose private to CST IV. We model the availability of unbound sialic acid as a function of bacteria-independent resource supply η_{Rp} and the density of CST IV bacteria that cleave off sialic acid from mucus sialoglycan. Thus, we express the realised input of CST IV private resource as $\eta_{Rp} \frac{C_4}{\theta + C_4}$ where θ represents the half-saturation constant of sialic acid cleaving. There is considerable variability in CST IV bacteria to cleave off and utilise sialic acid from bound sources (33). In our model, small θ represents strong sialidase activity, where the majority of bound sialic acid can be made available by a few CST IV bacteria. We carry out sensitivity analyses to explore the impact of θ (Supplementary Text S3).

b) *Inhibitory interactions mediated by lactic acid and other molecules.* Acidity is a key abiotic factor regulating microbial ecology in the vaginal environment (41). The acidity

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is primarily maintained by lactobacilli through the production of lactic acid during the fermentation of glycogen and its derivatives that fuels the majority of their growth (42). When dominated by lactobacilli, the vaginal milieu remains acidic with the pH ranging between 3.5 and 4.5. Acidity differentially affects bacterial communities. CST IV bacteria are commonly associated with vaginal pH > 4.5 as their growth is inhibited at a lower pH (8, 24). In contrast, lactobacilli have a higher tolerance to acidic conditions (with an inhibition pH below 4.0 (24, 25)). In our model, the lactic acid-mediated inhibitory effect on CST I and CST IV are denoted by $\alpha_{1,1}$ and $\alpha_{1,4}$, respectively, where $\alpha_{1,4} > \alpha_{1,1}$ because lactobacilli are more tolerant to acidic condition (21). We note that the inhibition rate $\alpha_{1,4}$ also encompasses other mechanisms through which CST I inhibits CST IV bacteria including hydrogen peroxide (H_2O_2) and bacteriocins (21). We ignore the reciprocal impact of CST IV to CST I ($\alpha_{4,1}$) as co-culture experiments have shown that *G. vaginalis* (CST IV) has negligible effects on *L. jensenii* (CST V, which is functionally akin to CST I) (43). Several CST IV bacteria have evolved defence mechanisms including biogenic amines synthesis, which elevates the extracellular pH and alleviates the acidic stress for themselves as well as other bacteria (26, 44). Thus, $\alpha_{1,4}$ includes the net effect of inhibition by CST I and counteracting defence mechanisms of CST IV.

Our vaginal microbiota model (Fig. 1) is described by the following set of equations:

$$\frac{\mathrm{d}C_1}{\mathrm{d}t} = -\gamma_C\ C_1 + \frac{\lambda_1\ R_s\ C_1}{\kappa + R_s} - \alpha_{1,1}\ C_1^2 \quad [2a]$$

$$\frac{\mathrm{d}C_4}{\mathrm{d}t} = -\gamma_C\ C_4 + \frac{\lambda_4\ (R_p + R_s)\ C_4}{\kappa + R_p + R_s} - \alpha_{1,4}\ C_1\ C_4 \quad [2b]$$

$$\frac{\mathrm{d}R_p}{\mathrm{d}t} = \eta_{Rp}\frac{C_4}{\theta + C_4} - \gamma_R\ R_p - \frac{\lambda_4\ R_p\ C_4}{\epsilon(\kappa + R_p + R_s)} \quad [2c]$$

$$\frac{\mathrm{d}R_s}{\mathrm{d}t} = \eta_{R_s} - \gamma_R\ R_s - \frac{\lambda_1\ R_s\ C_1}{\epsilon(\kappa + R_s)} - \frac{\lambda_4\ R_s\ C_4}{\epsilon(\kappa + R_p + R_s)} \quad [2d]$$

The subscripts 1 and 4 refer to CST I and CST IV bacteria and the subscripts p and s refer to private and shared resources, respectively.

Model restructuring. To facilitate model exploration, we first restructure the above model (eq. 2) into equations tracking the dynamics of the total bacterial ($C = C_1 + C_4$) and resource ($R = R_p + R_s$) densities and proportions that make up the CST IV bacteria ($q = \frac{C_4}{C}$) and their private resource ($p = \frac{R_p}{R}$). We then introduce χ, the proportion of newly supplied resource that is private to C_4 (such that $\eta_{R_p} = \chi\ \eta_R$ and $\eta_{R_s} = (1 - \chi)\ \eta_R$ where η_R is the overall supply). We also define ψ as the ratio of CST IV inhibition and self-inhibition (i.e., $\frac{\alpha_{1,4}}{\alpha_{1,1}}$).

We then set the time scale of the system relative to the CST I growth rate (λ_1) such that selected parameters become relative to it and variables are dimensionless (i.e., non-dimensionalisation). Next, we assume a separation of timescales between consumers and resources and solve for quasi-equilibrium conditions for resources such that the resource availability is held constant for a given density of consumers. In doing so, we now only explicitly track the consumer dynamics.

Details about making the model dimensionless can be found in Extended methods.

Clinical data. We took advantage of the previously published human vaginal microbiota and metabolomics data from a longitudinal clinical study (27) to parameterise the mechanistic ecological model and evaluate model predictions.

In particular, we could measure proxies for four of our variables. For the total amount of bacteria (C), the proxy was the ratio between the total bacterial DNA quantity in a sample and the median total bacterial DNA quantity in each of the samples using the qPCR data. For the proportion of CST IV bacteria (q), we used the proportion of CST IV-associated bacteria (here, the ones listed by the CST classification algorithm, VALENCIA (9)) in the 16S metabarcoding data. For the total amount of resources (R), wed use the sum of the abundance of four nutrients (glucose, maltose, maltotriose, and sialic acid) in a sample normalised by the median of these sums in all the samples using the metabolomics data. Finally, for the proportion of sialic acid among the resources (p), we used the ratio between the abundance of sialic acid and that of the four nutrients in the metabolomics data.

Details about the combination between the analytical expressions of the model and this data to parameterise the model can be found in Extended methods.

Participants and sample collection. Briefly, the study — originally published in Ravel et al. (27)— focused on investigating bacterial vaginosis and included 135 women from Birmingham, Alabama, USA. At the beginning of the study, participants underwent an assessment that included an extensive questionnaire on their medical, dental, obstetric, hygiene, sexual, and behavioural histories. They were also asked to self-collect three mid-vaginal swabs daily for ten weeks for use in genomic sequencing and metabolomics analysis. In addition, participants recorded their daily hygienic practices and sexual activities in a diary using a standardised form. Pelvic examinations were conducted at the time of enrolment and at weeks 5 and 10 or at interim times if the participant reported vaginal symptoms. Any symptomatic BV was diagnosed by the clinician and treated using a standard of BV care practices (45). Integration with our mechanistic model requires a sample to be processed for both genomic sequencing (16S metabarcoding and qPCR DNA quantity) and resource-related metabolomics profiling. In total, 540 samples from 82 women met our criteria.

Microbiota data: DNA was extracted from vaginal swabs and then the V3-V4 region of the bacterial 16S rRNA gene was amplified and sequenced on an Illumina HiSeq 2500 as described previously (46). The paired end sequences were then processed using DADA2 (47) generating amplicon sequence variants (ASVs). The ASVs were then assigned taxonomy using a combination of the RDP Naive Bayesian Classifier (48) trained on the SILVA 16S rRNA gene database (49) and speciateIT software (50). Finally, community state types (CSTs) were assigned using VALENCIA software (9). The total bacterial DNA was quantified using qPCR. We normalised the bacterial DNA quantity with the median total qPCR quantity of all samples such that the default value ($C = 1$) corresponds to the study median as explained above.

Metabolomics data: Vaginal swabs were also processed by Metabolon for global liquid chromatography-mass spectrometry (LC-MS) metabolomic profiling, which provides information roughly proportional to the true concentration of the metabolites in a sample. Metabolomics readings were batch-standardised by Metabolon. An important limitation of global metabolomic profiling is that it provides an imperfect reflection of the metabolite quantity in a sample. Specifically, the Pearson's correlation coefficient between the raw global metabolomics output and concentrations measured by the targeted metabolomics approach (which offers the most accurate quantitative information) is generally around 0.7 (51). As metabolites are small molecules less than 1.5 kDa in size (52), whole glycogen molecules are not detected by metabolomics profiling. Thus, we focused on three glycogen breakdown products (namely, glucose, maltose, and maltotriose) as a proxy for the shared resource. We refer to the sum of these three metabolites as glycogen derivatives. As a proxy for the private resource used by CST IV, we used N-acetylneuraminate, the anionic form of the acetylneuraminic acid (Neu5Ac), which is the form of sialic acid found in the vaginal environment (33). With the aforementioned caveat that global metabolomic profiling provides an imperfect reflection of metabolite quantity, we use resource-related metabolomics data in two ways: total resource-related metabolite quantity (i.e., the sum of glucose, maltose, maltotriose and sialic acid) and proportion of CST IV private resource (i.e., sialic acid relative to the total resource quantity). We normalised raw resource metabolite values by the total resource-related metabolites across all samples such that the default total resource value ($R = 1$) corresponds to the study median.

Evaluating model predictions in light of clinical data. To corroborate the role of resources in shaping real vaginal microbiota communities, we graphically explored the relationship between the empirically

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informed proportion of CST IV private resources (χ; see equation 8b in Extended Methods S1) and CST classification. We also visualised CST classification as a function of shared productivity (i.e., yield-adjusted glycogen derivative supply, i.e., $\overline{\tau}(1-\chi)$) and private productivity (i.e., yield-adjusted sialic acid supply, $\overline{\tau}\ \chi$) to explore the influence of the absolute resource supply in shaping bacterial community composition. As the half-saturation constants (i.e., κ and θ) are not precisely informed by data, we do not rely on the absolute value of $\overline{\tau}$ and χ. Nonetheless, our sensitivity analyses demonstrate that the rank order of $\overline{\tau}$ and χ estimates are largely consistent across a range of θ and κ such that our findings are qualitatively unaffected except in the case of very large θ such that private resources are virtually inaccessible. (Supplementary Text S3).

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Data and software programmes used in this study are provided as Auxiliary files. Amplicon sequence data used in this study are available in the NCBI Short Read Archive (SRA) deposited under the BioProject PRJNA208535. Vaginal shotgun metagenomics data used to estimate *in vivo* growth rates can be found in the NCBI SRA under the BioProject PRJNA797778.

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