Microbiota vaginale

di

CRISTIANO ALEX DE MARZI


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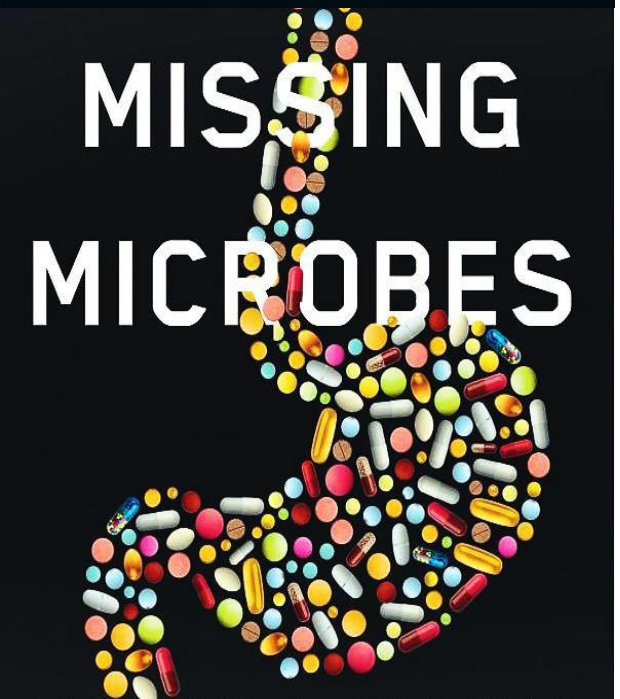
MISSING
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Bacteria make us sick. Do they also keep us alive?
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nature
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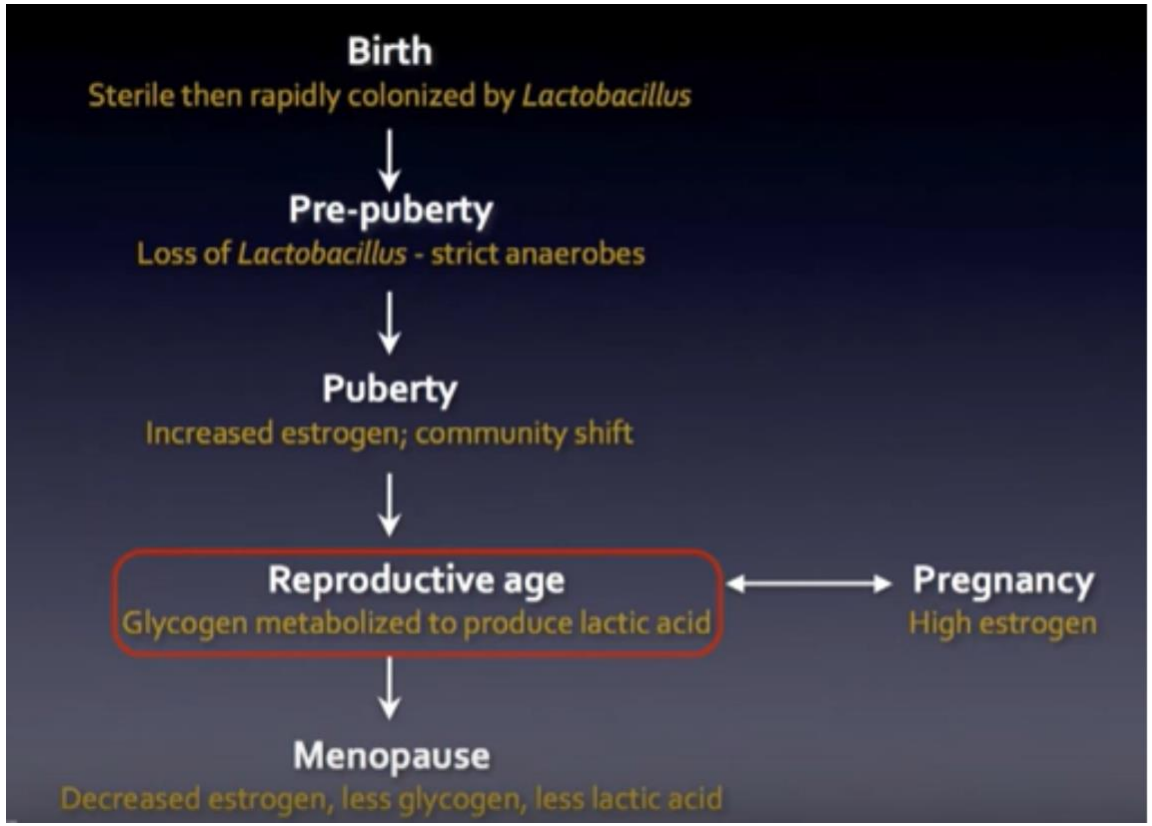
Body microbes outnumber our own cells ten to one — it's time we got to know our fellow travellers
PAGES 194,207 & 209
THE HUMAN MICROBIOME

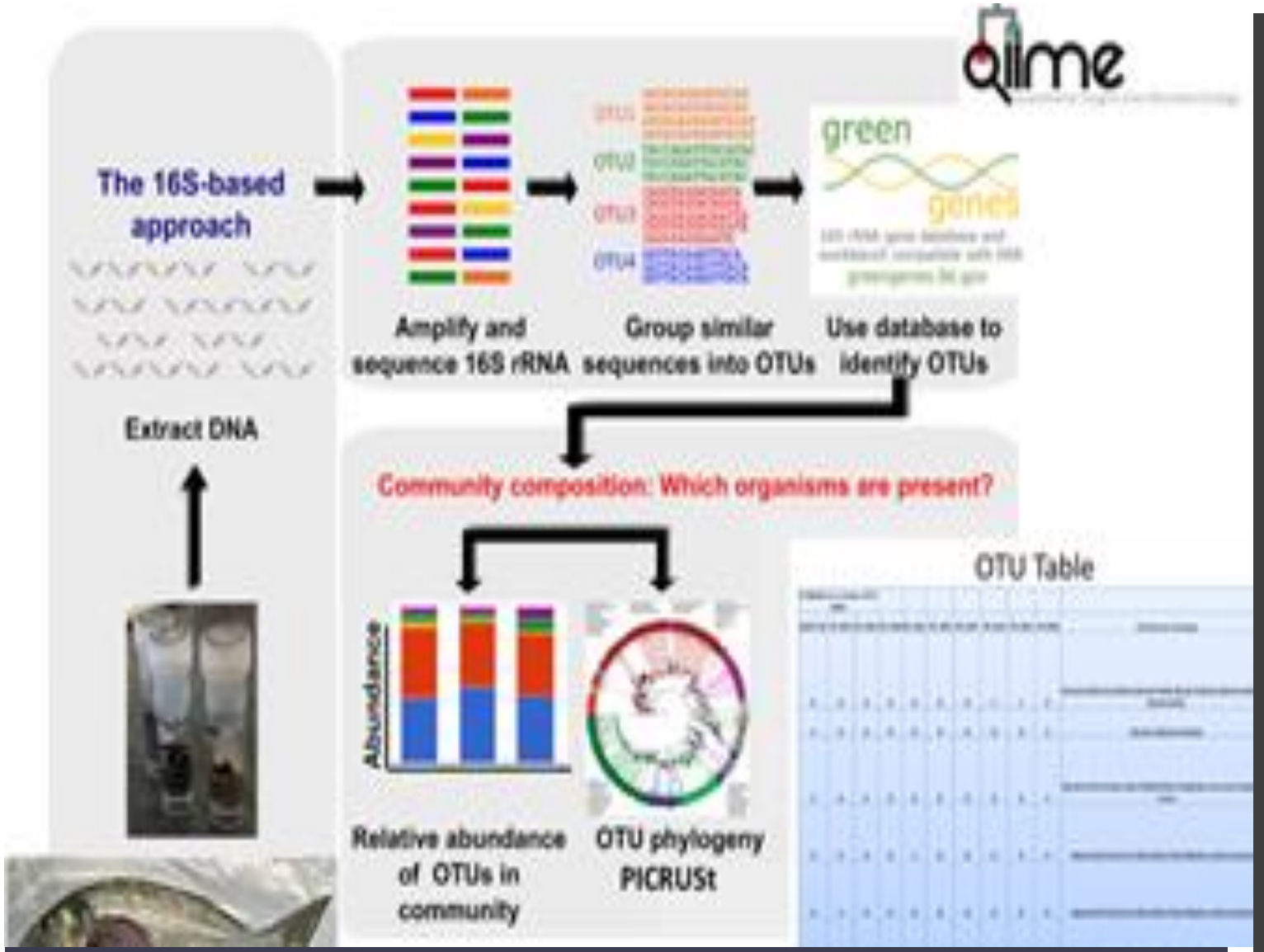
Conoscenze classiche sull'ambiente vaginale

- Lactobacillus spp sono i i normali abitatori del microbiota vaginale una donna in età riproduttiva.
- La possibilità di sviluppo di altri batteri , compresi i patogeni è limitata.
- Il processo difensivo non è del tutto noto:
  - pH 4-4,5
  - Lattati
  - Altri ac grassi
  - H_2O_2 ?
  - Batteriocine
  - altro

- **Döderlein, Albert Sigmund** Medico tedesco (Augusta 1860 - Monaco di Baviera 1941). Direttore della clinica ostetrico ginecologica di Monaco (dal 1907) il primo a descrivere i bacilli vaginali

The vaginal microbiota throug the lifespan





NGS

- Si analizzano utilizzando tecniche innovative definite **Next Generation Sequencing (NGS)** che hanno dato un notevole impulso alla caratterizzazione del microbiota umano e della sua complessità. Queste tecniche sono in grado di sfruttare la particolare conformazione della sequenza di acidi nucleici che caratterizza il patrimonio genetico della flora commensale. Si basano sull'amplificazione mediante PCR e sequenziamento di alcune regioni variabili di geni da cui derivano le sequenze di rRNA 16S (16S rDNA, DNA ribosomiale 16S). Tali regioni sono infatti, specie specifiche e il loro sequenziamento, permette di identificare e differenziare le diverse specie Questo tipo di analisi prevede l'estrazione del 16S rDNA da matrici complesse, come ad esempio i campioni fecali, l'amplificazione via PCR del gene 16S con l'utilizzo di primer universali e il sequenziamento , in un'unica soluzione. Si generano in questo modo milioni di sequenze le quali sono poi elaborate tramite software dedicati in grado di fare sia un'analisi tassonomica delle sequenze ottenute che un'analisi funzionale del microbioma.
-

NIH:
The Human Microbioma Project Consortium
Nature, vol 486 ;
14 June 2012

ARTICLE

doi:10.1038/nature11234

Structure, function and diversity of the healthy human microbiome

The Human Microbiome Project Consortium*

Studies of the human microbiome have revealed that even healthy individuals differ remarkably in the microbes that occupy habitats such as the gut, skin and vagina. Much of this diversity remains unexplained, although diet, environment, host genetics and early microbial exposure have all been implicated. Accordingly, to characterize the ecology of human-associated microbial communities, the Human Microbiome Project has analysed the largest cohort and set of distinct, clinically relevant body habitats so far. We found the diversity and abundance of each habitat's signature microbes to vary widely even among healthy subjects, with strong niche specialization both within and among individuals. The project encountered an estimated 81–99% of the genera, enzyme families and community configurations occupied by the healthy Western microbiome. Metagenomic carriage of metabolic pathways was stable among individuals despite variation in community structure, and ethnic/racial background proved to be one of the strongest associations of both pathways and microbes with clinical metadata. These results thus delineate the range of structural and functional configurations normal in the microbial communities of a healthy population, enabling future characterization of the epidemiology, ecology and translational applications of the human microbiome.

A total of 4,788 specimens from 242 screened and phenotyped adults[1] (129 males, 113 females) were available for this study, representing the majority of the target Human Microbiome Project (HMP) cohort of 300 individuals. Adult subjects lacking evidence of disease were recruited based on a lengthy list of exclusion criteria; we will refer to them here as 'healthy', as defined by the consortium clinical sampling criteria (K. Aagaard *et al.*, manuscript submitted). Women were sampled at 18 body habitats, men at 15 (excluding three vaginal sites), distributed among five major body areas. Nine specimens were collected from the oral cavity and oropharynx: saliva; buccal mucosa (cheek), keratinized gingiva (gums), palate, tonsils, throat and tongue soft tissues, and supra- and subgingival dental plaque (tooth biofilm above and below the gum). Four skin specimens were collected from the two retroauricular creases (behind each ear) and the two antecubital fossae (inner elbows), and one specimen for the anterior nares (nostrils). A self-collected stool specimen represented the microbiota of the lower gastrointestinal tract, and three vaginal specimens were collected from the vaginal introitus, midpoint and posterior fornix. To evaluate within-subject stability of the microbiome, 131 individuals in these data were sampled at an additional time point (mean 219 days and s.d. 69 days after first sampling, range 35–404 days). After quality control, these specimens were used for 16S rRNA gene analysis via 454 pyrosequencing (abbreviated henceforth as 16S profiling, mean 5,408 and s.d. 4,605 filtered sequences per sample); to assess function, 681 samples were sequenced using paired-end Illumina shotgun metagenomic reads (mean 2.9 gigabases (Gb) and s.d. 2.1 Gb per sample)[2]. More details on data generation are provided in related HMP publications[4] and in Supplementary Methods.

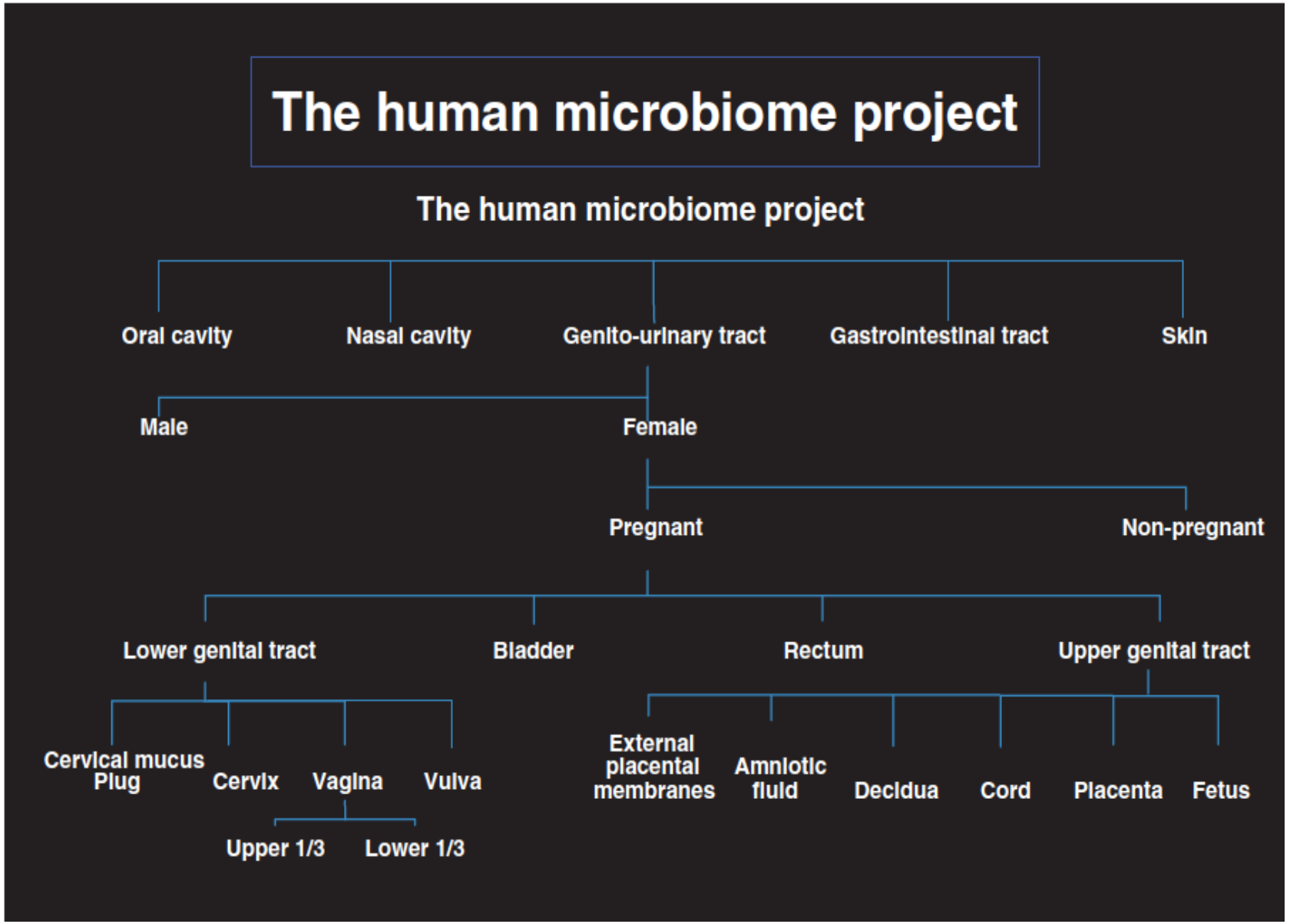
Microbial diversity of healthy humans

The diversity of microbes within a given body habitat can be defined as the number and abundance distribution of distinct types of organisms, which has been linked to several human diseases: low diversity in the gut to obesity and inflammatory bowel disease[2,3], for example, and high diversity in the vagina to bacterial vaginosis[5]. For this large study involving microbiome samples collected from healthy volunteers at two distinct geographic locations in the United States, we have defined the microbial communities at each body habitat, encountering 81–99% of predicted genera and saturating the range of overall community configurations (Fig. 1, Supplementary Fig. 1 and Supplementary Table 1; see also Fig. 4). Oral and stool communities were especially diverse in terms of community membership, expanding prior observations[3], and vaginal sites harboured particularly simple communities (Fig. 1a). This study established that these patterns of alpha diversity (within samples) differed markedly from comparisons between samples from the same habitat among subjects (beta diversity, Fig. 1b). For example, the saliva had among the highest median alpha diversities of operational taxonomic units (OTUs, roughly species level classification, see http://hmpdacc.org/HMQCP), but one of the lowest beta diversities—so although each individual's saliva was ecologically rich, members of the population shared similar organisms. Conversely, the antecubital fossae (skin) had the highest beta diversity but were intermediate in alpha diversity. The vagina had the lowest alpha diversity, with quite low beta diversity at the genus level but very high among OTUs due to the presence of distinct *Lactobacillus* spp. (Fig. 1b). The primary patterns of variation in community structure followed the major body habitat groups (oral, skin, gut and vaginal), defining as a result the complete range of population-wide between-subject variation in human microbiome habitats (Fig. 1c). Within-subject variation over time was consistently lower than between-subject variation, both in organismal composition and in metabolic function (Fig. 1d). The uniqueness of each individual's microbial community thus seems to be stable over time (relative to the population as a whole), which may be another feature of the human microbiome specifically associated with health.

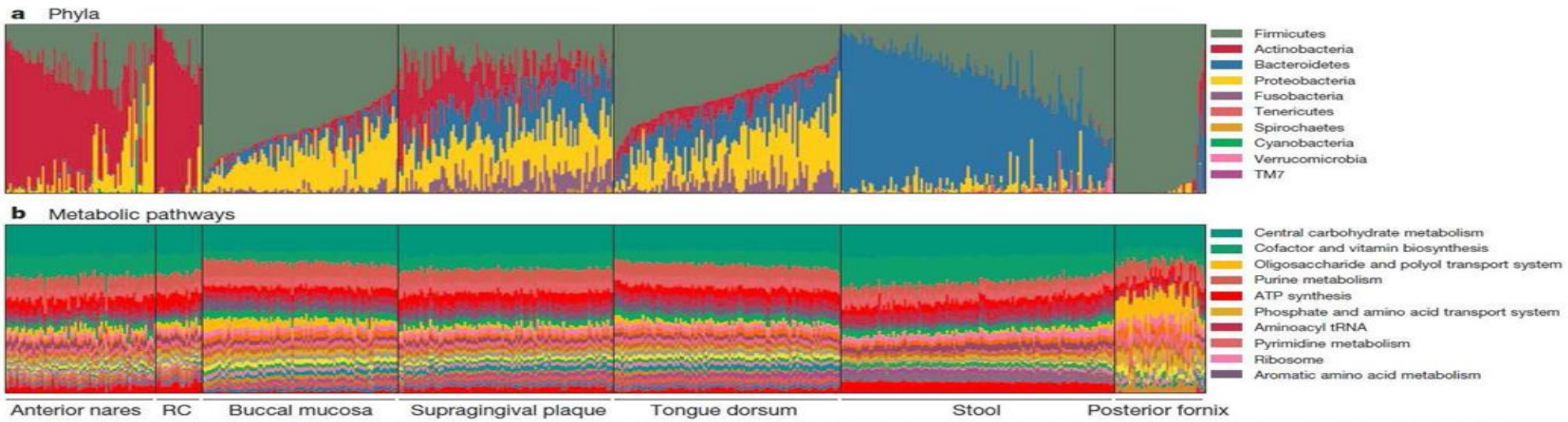
No taxa were observed to be universally present among all body habitats and individuals at the sequencing depth employed here, unlike several pathways (Fig. 2 and Supplementary Fig. 2, see below), although several clades demonstrated broad prevalence and relatively abundant carriage patterns[6,7]. Instead, as suggested by individually

*Lists of participants and their affiliations appear at the end of the paper.

National Institute of Health (2008)



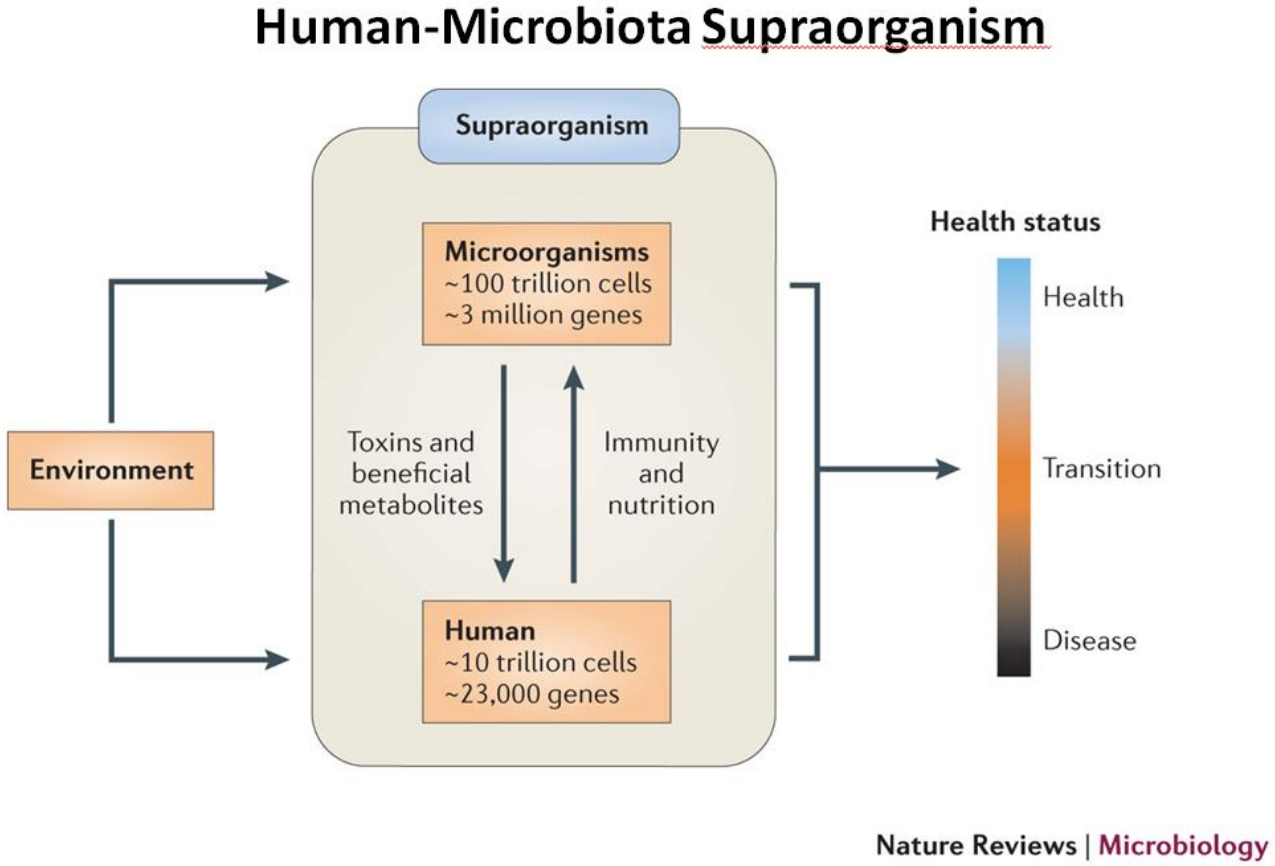
Human Microbiome Project



HMP, Nature 2012

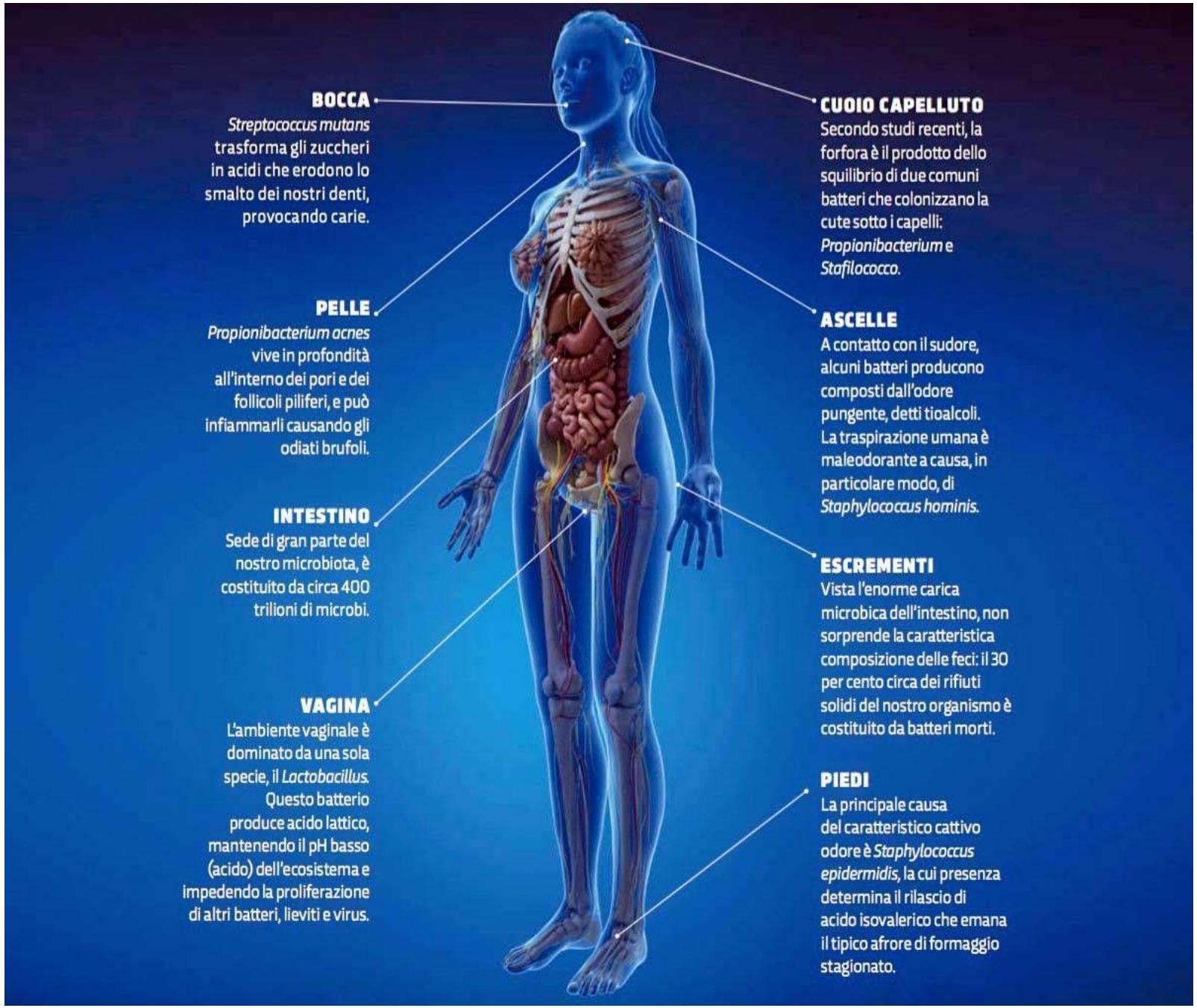
- Each site is different in terms of its predominant microbial types
- No core microbiome at every site for everyone
- Considerable variation in health
- Unique fingerprints at each site for individuals
- Generally similar functionality
- Loss and gain of functions at the individual level with strains

Nuovo Organo o Superorganismo?

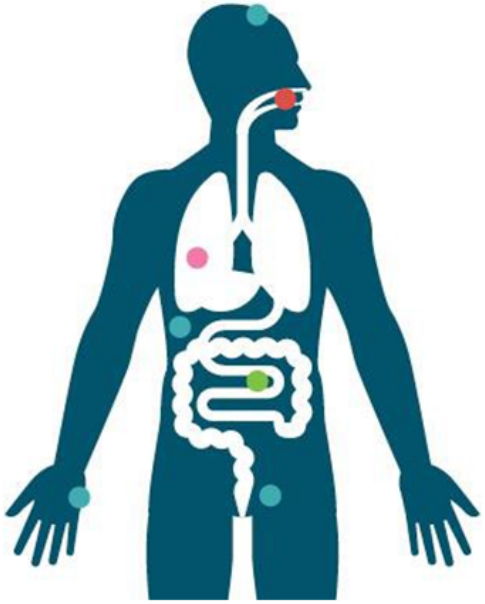


Nature Reviews Microbiology 11, 639–647 2013

Nuovo Organo o Superorganismo?



The Human Mycobiome



ORAL CAVITY

- *Alternaria*
- *Aspergillus*
- *Aureobasidium*
- *Candida*
- *Cladosporium*
- *Cryptococcus*
- *Fusarium*
- *Gibberella*
- *Glomus*
- *Pichia*
- *Saccharomyces*
- *Teratosphaeria*

LUNGS

- *Aspergillus*
- *Candida*
- *Cladosporium*
- *Penicillium*
- *Cryptococcus*

GASTRO-INTESTINAL

- *Aspergillus*
- *Candida*
- *Cladosporium*
- *Cryptococcus*
- *Fusarium*
- *Penicillium*
- *Pneumocystis*
- *Mucor*
- *Saccharomyces*

SKIN

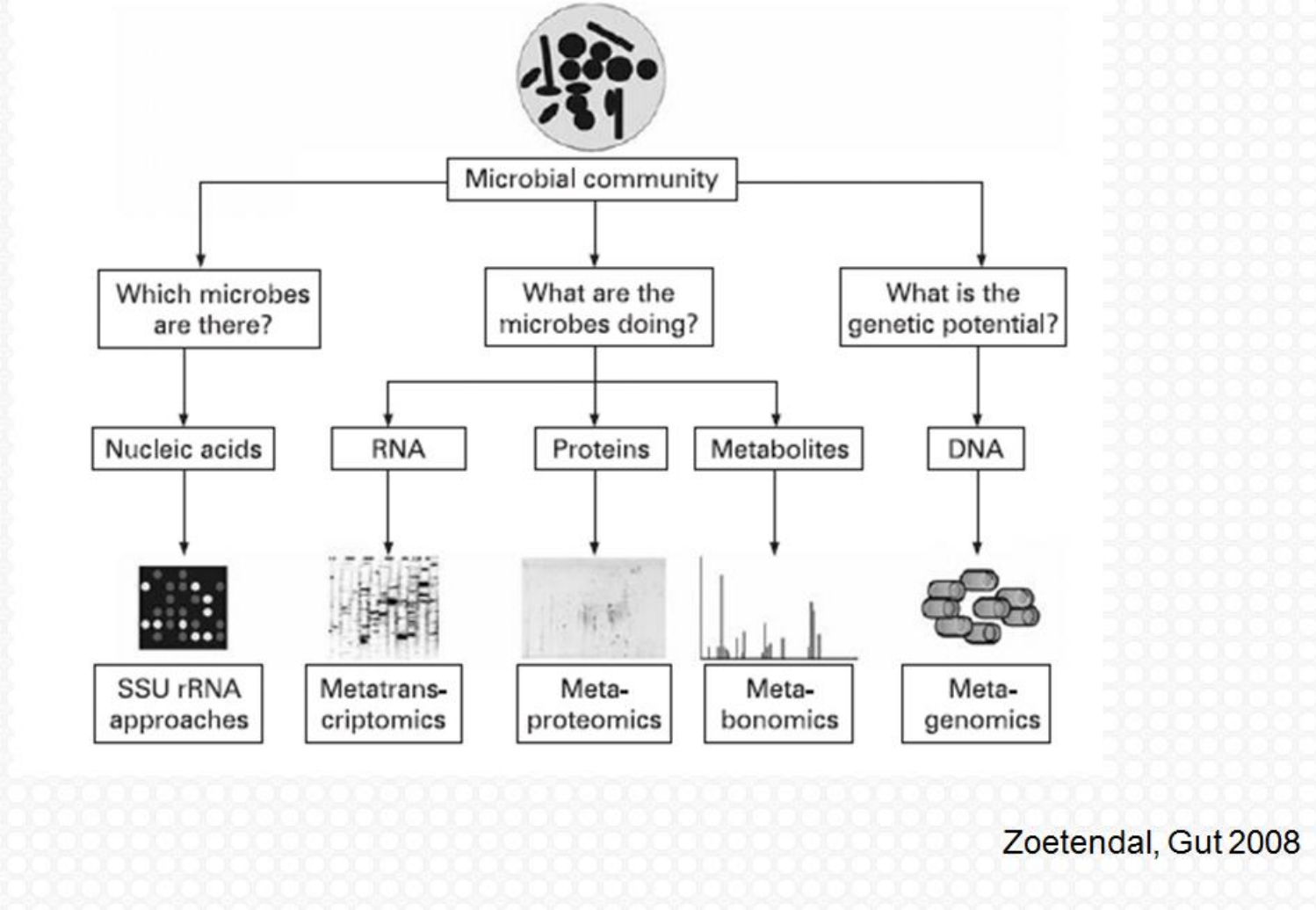
- *Candida*
- *Cryptococcus*
- *Debaryomyces*
- *Epidermophyton*
- *Malassezia*
- *Microsporum*
- *Rhodotorula*
- *Trichophyton*
- *Aspergillus*
- *Chrysosporium*
- *Epicoccum*
- *Leptosphaerulina*
- *Penicillium*
- *Phoma*
- *Saccharomyces*
- *Ustilago*

*Potentially pathogenic lineages

- Early surveys have revealed several pathogenic species that may increase one's risk of disease when the healthy microbiome is disrupted.
- *Candida* and *Aspergillus* species are among the most common members of the human mycobiome.
- When the balance of a microbial community is disrupted, fungal species can flourish and cause disease

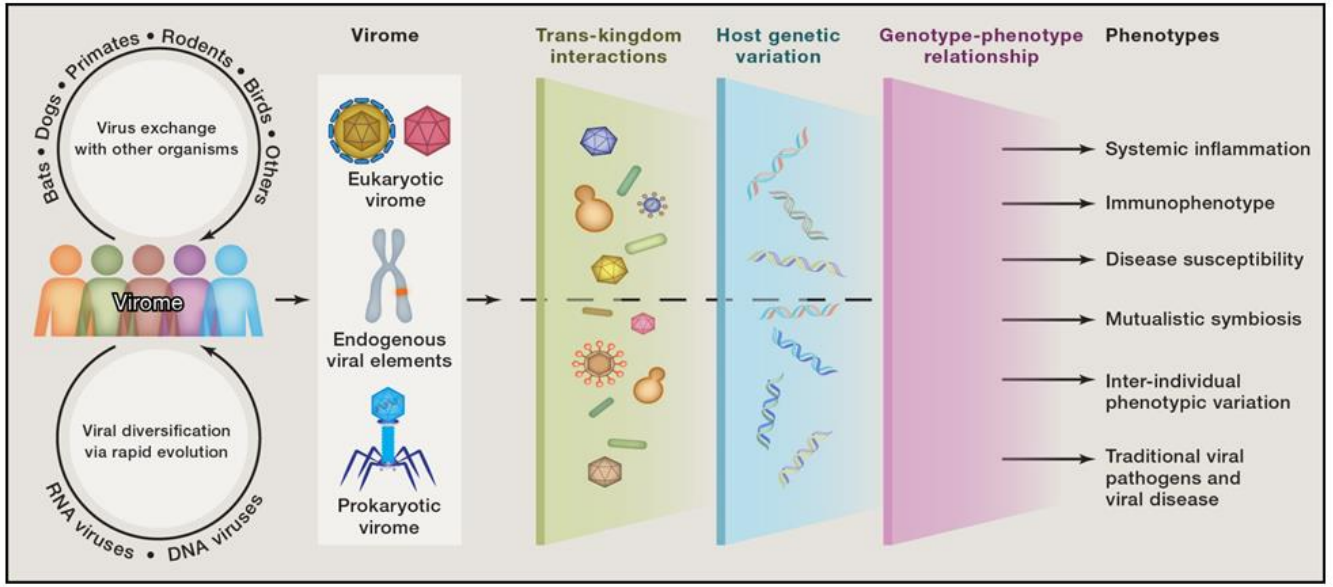
The Scientist. 02.2016. 37

New way?



Zoetendal, Gut 2008

Particular Interest in the Virome



Virgin et al., 2014 Cell 157:142

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PERSPECTIVE

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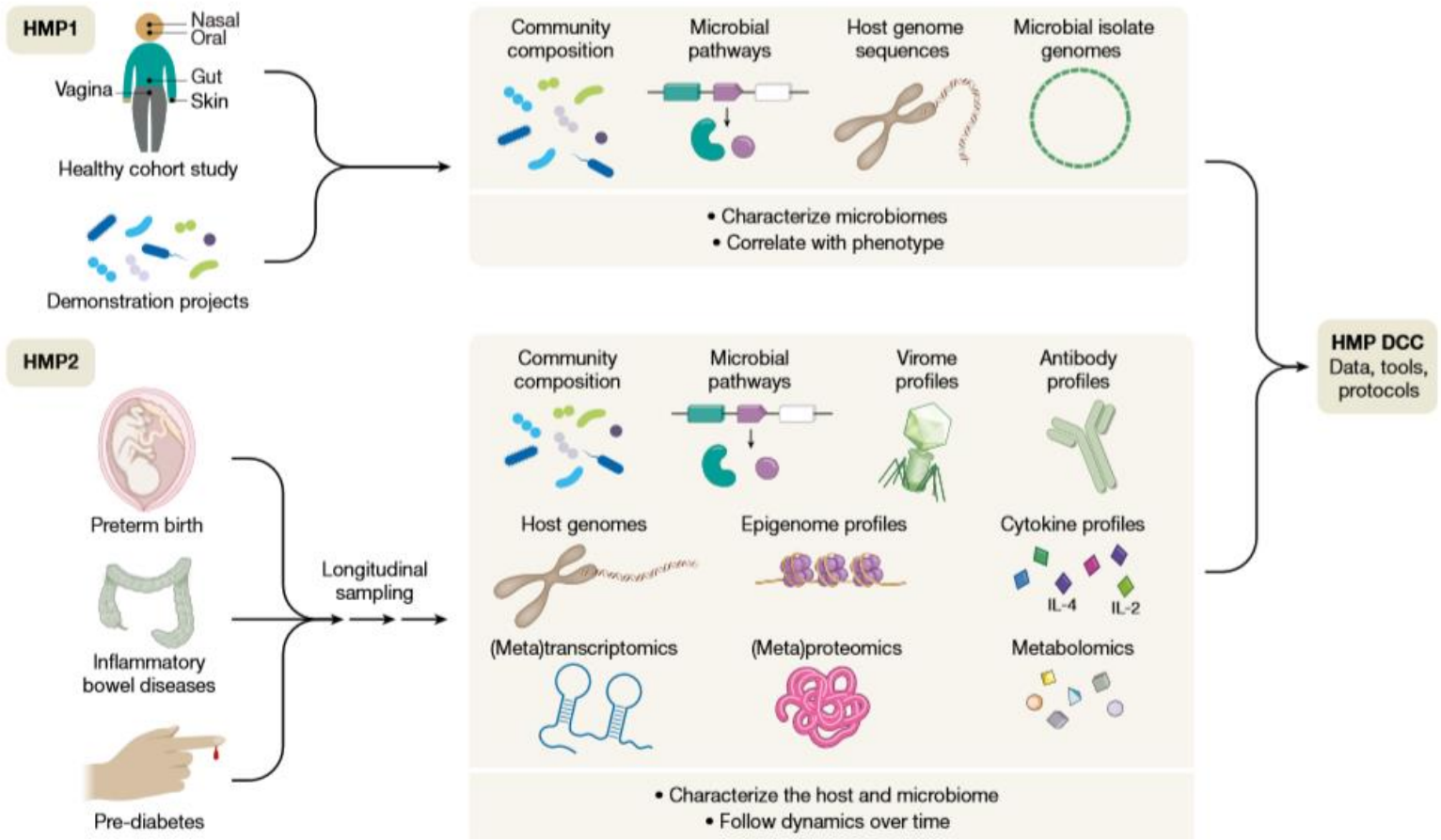
The Integrative Human Microbiome Project

The Integrative HMP (iHMP) Research Network Consortium*

The NIH Human Microbiome Project (HMP) has been carried out over ten years and two phases to provide resources, methods, and discoveries that link interactions between humans and their microbiomes to health-related outcomes. The recently completed second phase, the Integrative Human Microbiome Project, comprised studies of dynamic changes in the microbiome and host under three conditions: pregnancy and preterm birth; inflammatory bowel diseases; and stressors that affect individuals with prediabetes. The associated research begins to elucidate mechanisms of host–microbiome interactions under these conditions, provides unique data resources (at the HMP Data Coordination Center), and represents a paradigm for future multi-omic studies of the human microbiome.

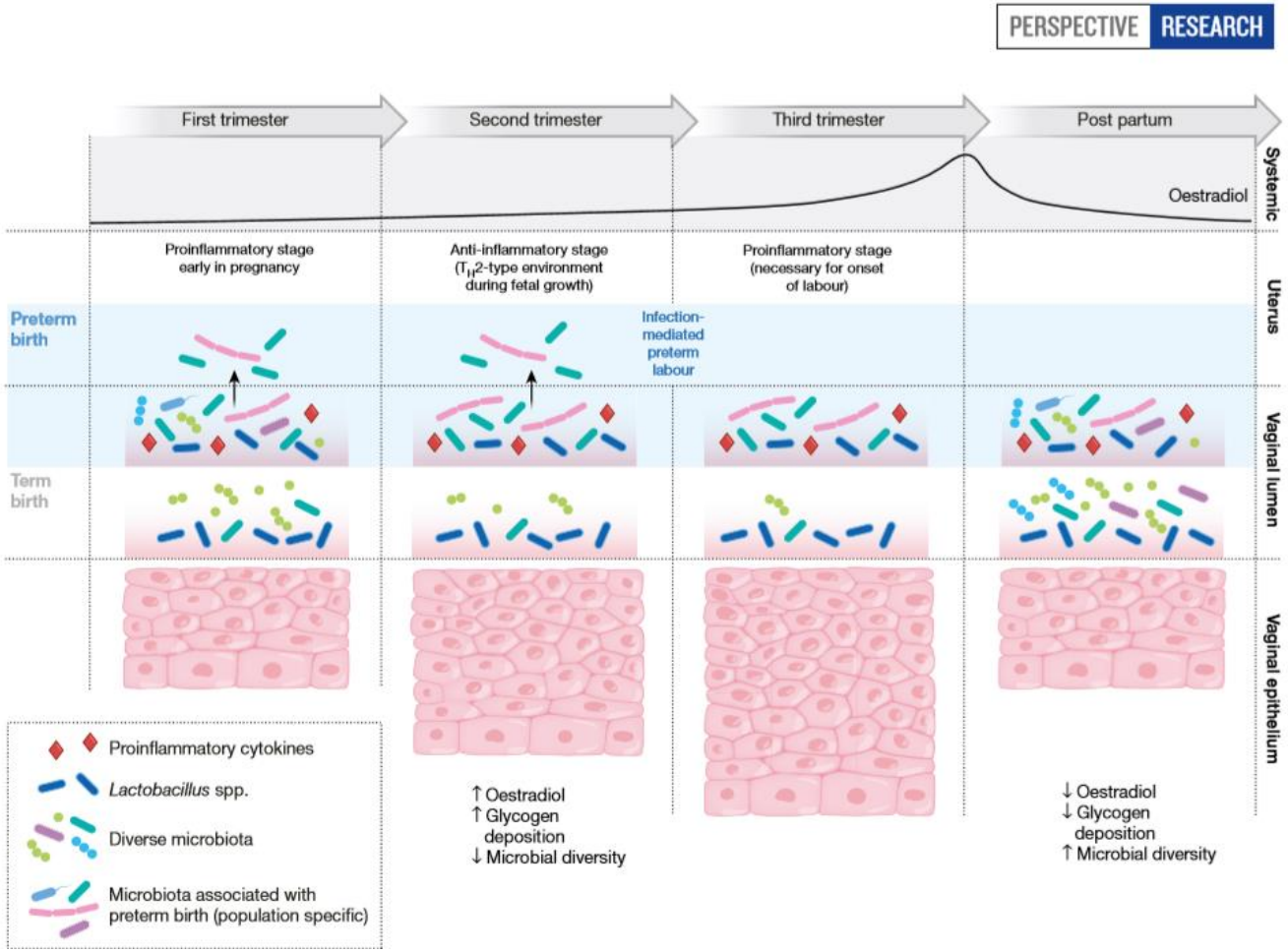
RESEARCH PERSPECTIVE



The Multi-Omic Microbiome Study: Pregnancy Initiative (MOMS-PI)

- | The vaginal microbiome and its relationships with host factors in pregnancy and preterm birth. The MOMS-PI project followed 1,527 pregnancies longitudinally and involved the collection of 206,437 biospecimens for analysis of host and microbial factors (16S amplicon, metagenomic, and metatranscriptomic sequencing; cytokine profiling; metabolomics; proteomics; genomics; and microbial isolate culture). Around 600 pregnancies were analysed in depth to assess features that lead to preterm birth; this analysis identified both host (for example, cytokine) and microbial (for example, ecological and specific strain) factors.
- As pregnancy progresses, with predictable changes in systemic oestradiol levels, the uterine and vaginal environments undergo various changes. The uterus switches from an early pro-inflammatory condition to an antiinflammatory condition in the second trimester, and then back to a proinflammatory condition before the onset of labour. Meanwhile, specific changes in the microbiome of the vaginal lumen can be associated with preterm birth, possibly through mechanisms involving microorganisms travelling from the vagina to the uterus. The figure depicts an overview of longitudinal changes in the vaginal mucosal ecosystem and uterus during pregnancy.

The Multi-Omic Microbiome Pregnancy Initiative (MOMS-PI)



Microbiota Vaginale

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Exhaustive repertoire of human vaginal microbiota

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ABSTRACT

Bacteria that colonize the vaginal microbiota of women play an important role in health and homeostasis. Disruption of the proportion of bacteria predisposes to dysbiosis like bacterial vaginosis or severe gynecological conditions such as preterm birth, pelvic inflammatory disease and also sexually transmitted diseases. Knowledge about normal and abnormal vaginal microbiota has become a little clearer in recent years. Culture techniques have made it possible to isolate and describe many bacterial species, whereas molecular methods have highlighted the limits of culture by showing that the vagina was a complex ecosystem containing a wide range of non-cultured or difficult-to-identify bacteria. Based on an exhaustive review of the scientific literature, we built the repertoire of all the bacteria found using culture-based and/or independent methods on the human vagina. So, whether they are valid or not, we inventoried 581 bacteria identified in the human vagina distributed into 10 taxa, mainly in the phyla of *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, and *Proteobacteria* with 206 distinct genera classified in 96 different families. This repertoire is essential for microbiologists and clinicians and represents the starting point for a Vaginal Microbiome Project such a project aimed to map the human vaginal microbiota, to better understand the dysbioses or infections caused by its imbalance in order to offer more appropriate treatments.

1. Introduction

Microbiota associated with the human body (skin, mucosal membranes of the respiratory airways, oral cavity, gastrointestinal, urinary, and genital tracts) has a considerable influence on human development, physiology, and immunity [1,2]. It is estimated that the number of microorganisms in the human microbiome are teen times higher than nucleated cells [3]. Members of the microbial communities associated with humans interact between them and their host to form a stable ecosystem that responds to disturbances [4]. This mutualistic relationship constitutes the first line of defense by inhibiting and preventing the growth of pathogens [4]. Thus, to characterize the normal human microbiota, various body samples including skin, nose, mouth, gastrointestinal tract, and vagina from healthy individuals were analyzed [3].

The vaginal microbiome harbors diverse communities of microorganisms, known as vaginal flora which has an important impact on women's health as well as that of their newborns [5]. Bacteria dominate largely vaginal microbiome. A woman in childbearing age produces approximately 1–4 ml of vaginal fluid that contains 10^6 to 10^8 bacterial vaginal microbiota have increased and the advances in technology, including molecular techniques as well as new OMICS strategies, have demonstrated its involvement in reproductive health [1,7–12]. The composition of the vaginal microbiota depends on age, menstruations, hormonal fluctuations, sexual behaviors, and also the use of drugs such as probiotics and antibiotics causing its imbalance [13–16]. As part of the human microbiome project, the study of the vaginal microbiome has shown a relationship between bacteria present in the vagina and diseases. The imbalance in the composition of the vaginal microbiota can lead to dysbiosis such as bacterial vaginosis [16,17]. Thus, the knowledge of vaginal microbiota composition is required to better understand this vaginal condition but also the host-microbiota interactions.

In addition to the microbiota constituents, fungal communities (mycobiome) [18] and viral populations (virome) [19] are also an important part of the vaginal microbiome and have relationships with vaginal bacterial components. These underestimated microbiomes play a role in health and diseases such as candidiasis due to an overgrowth of *Candida albicans* [18] and preterm birth caused by a higher viral vaginal diversity [19].

Exhaustive repertoire of human vaginal microbiota

Diop K, Dufour J, Levasseur A, Fenollar F
Human Microbiome Journal
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- It is the starting point for a Vaginal Microbiome Project aiming to characterize as fully possible the human vaginal microbiota of normal and bacterial vaginosis floras, to better understand this dysbiosis and better manage this public health problem.

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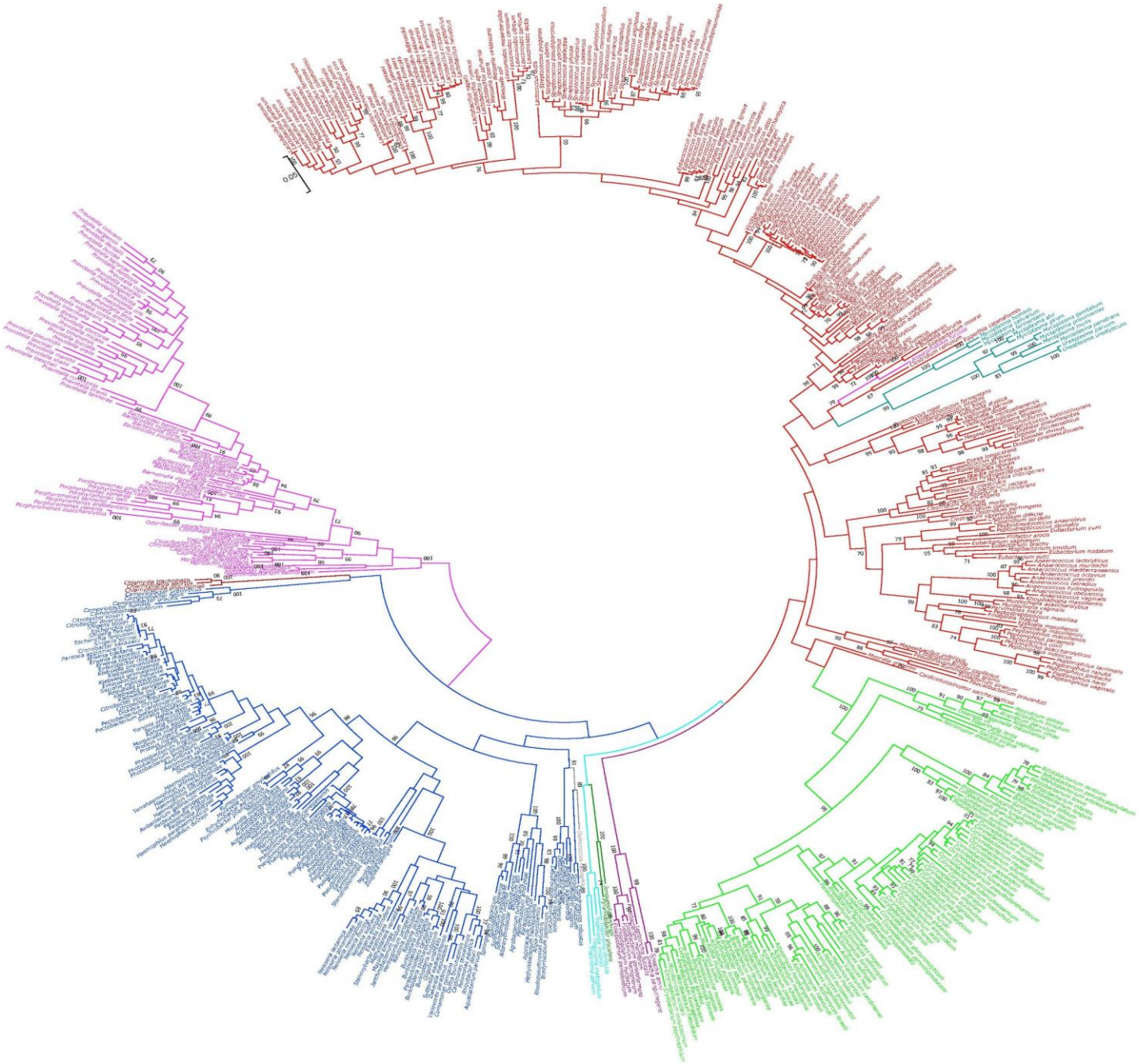

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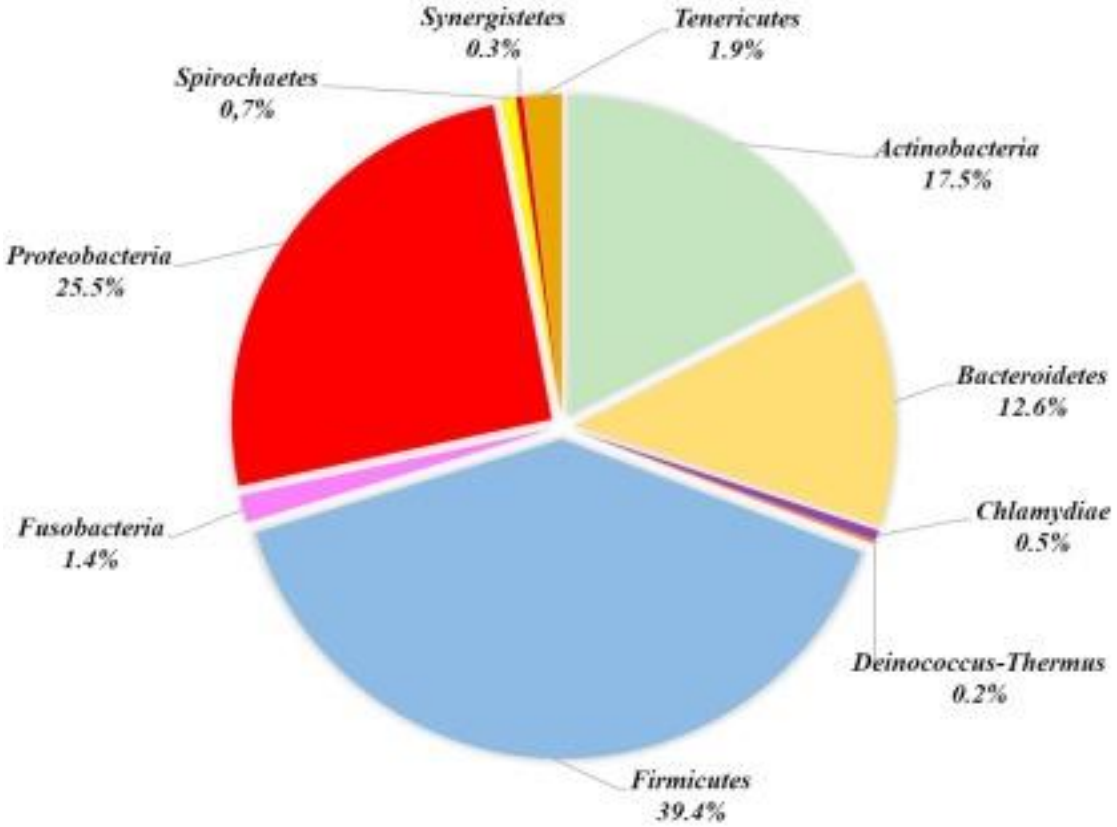

Proc. Natl. Acad.Sci. US

March15,2011: vol 108

Ravel J., Gajer P., et alii.

Vaginal microbiome of reproductive-age women

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Edited by Jeffrey I. Gordon, Washington University School of Medicine, St. Louis, MO, and approved May 7, 2010 (received for review March 14, 2010)

The means by which vaginal microbiomes help prevent urogenital diseases in women and maintain health are poorly understood. To gain insight into this, the vaginal bacterial communities of 396 asymptomatic North American women who represented four ethnic groups (white, black, Hispanic, and Asian) were sampled and the species composition characterized by pyrosequencing of barcoded 16S rRNA genes. The communities clustered into five groups: four were dominated by *Lactobacillus iners*, *L. crispatus*, *L. gasseri*, or *L. jensenii*, whereas the fifth had lower proportions of lactic acid bacteria and higher proportions of strictly anaerobic organisms, indicating that a potential key ecological function, the production of lactic acid, seems to be conserved in all communities. The proportions of each community group varied among the four ethnic groups, and these differences were statistically significant [$\chi^2(10) = 36.8$, $P < 0.0001$]. Moreover, the vaginal pH of women in different ethnic groups also differed and was higher in Hispanic (pH 5.0 ± 0.59) and black (pH 4.7 ± 1.04) women as compared with Asian (pH 4.4 ± 0.59) and white (pH 4.2 ± 0.3) women. Phylotypes with correlated relative abundances were found in all communities, and these patterns were associated with either high or low Nugent scores, which are used as a factor for the diagnosis of bacterial vaginosis. The inherent differences within and between women in different ethnic groups strongly argues for a more refined definition of the kinds of bacterial communities normally found in healthy women and the need to appreciate differences between individuals so they can be taken into account in risk assessment and disease diagnosis.

microbial communities | ecology | human microbiome | women's health | bacterial vaginosis

The human body harbors microorganisms that inhabit surfaces and cavities exposed or connected to the external environment. Each body site includes ecological communities of microbial species that exist in a mutualistic relationship with the host. The kinds of organisms present are highly dependent on the prevailing environmental conditions and host factors and hence vary from site to site. Moreover, they vary between individuals and over time (1). The human vaginal microbiota seem to play a key role in preventing a number of urogenital diseases, such as bacterial vaginosis, yeast infections, sexually transmitted infections, urinary tract infections (2–9), and HIV infection (10, 11). Common wisdom attributes this to lactic acid–producing bacteria, mainly *Lactobacillus* sp., that commonly inhabit the vagina. These species are thought to play key protective roles by lowering the environmental pH through lactic acid production (12, 13), by producing various bacteriostatic and bacteriocidal compounds, or through competitive exclusion (13–16). The advent of culture-independent molecular approaches based on the cloning and sequencing of 16S rRNA genes has furthered our understanding of the vaginal microbiota by identifying taxa that had not been cultured (17–24). However, this technique is limited by high cost and low throughput, hence only small numbers of samples have usually been analyzed, and the depth of sample analysis was not great.

In this study we sought to develop an in-depth and accurate understanding of the composition and ecology of the vagina microbial ecosystem in asymptomatic women using a high-throughput method based on pyrosequencing of barcoded 16S rRNA genes. The data obtained are an essential prerequisite for comprehending the role and ultimately the function of vaginal microbiota in reducing the risk of acquiring diseases and identifying factors that determine disease susceptibility. Specifically we sought to characterize the vaginal microbial communities in a cohort of 396 North American women equally representing four ethnic backgrounds (Asian, white, black, and Hispanic) and further address three aims. The first was to establish whether there were correlations between community composition and vaginal pH because these would be indicative of community performance. The second was to explore how the species composition of vaginal communities was reflected in Nugent scores (25), a diagnostic factor commonly used to identify women with bacterial vaginosis (26). Finally, the third aim was to identify patterns in the relative abundances of different species because these might reflect antagonistic or cooperative interspecies interactions.

Results and Discussion

We characterized the vaginal microbiota and vaginal pH of 396 asymptomatic, sexually active women who fairly equally represented four self-reported ethnic groups: white ($n = 98$), black ($n = 104$), Asian ($n = 97$), and Hispanic ($n = 97$). The demographics and other characteristics of the women are given in Table S1. Each woman used two swabs to self-collect midvaginal samples. One swab was used to evaluate the vaginal microbiota on the basis of the Nugent criteria used for the diagnosis of bacterial vaginosis (25), and the second was used in procedures to determine the species composition and structure of the resident bacterial communities (27). The latter was accomplished by phylogenetic analysis of 16S rRNA gene sequences (28). Whole-genomic DNA was extracted from each swab, and variable regions 1 and 2

This paper results from the Arthur M. Sackler Colloquium of the National Academy of Sciences, "Microbes and Health" held November 2–3, 2009, at the Arnold and Mabel Beckman Center of the National Academies of Sciences and Engineering in Irvine, CA. The complete program and audio files of most presentations are available on the NAS Web site at http://www.nasonline.org/SACKLER_Microbes_and_Health.

Author contributions: J. Ravel, R.M.B., C.C.D., K.A., and L.J.F. designed research; J. Ravel, P.G., Z.A., R.M.B., and L.J.F. analyzed data; P.G. contributed new reagents/analytic tools; G.M.S., S.L.M., S.S.K.K., S.K., R.G., J. Russell, C.O.T., K.A., and L.P. performed research; and J. Ravel, P.G., and L.J.F. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

Data deposition: The bacterial 16S rRNA gene sequences have been deposited in the National Center for Biotechnology Information Short Read Archive (SRA022855).

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The vaginal microbiome: rethinking health and diseases

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[2]Department of Biological Sciences and the Initiative for Bioinformatics and Evolutionary Studies, University of Idaho, Moscow, ID 83844

Abstract

Vaginal microbiota form a mutually beneficial relationship with their host and have major impact on health and disease. In recent years our understanding of vaginal bacterial community composition and structure has significantly broadened as a result of investigators using cultivation-independent methods based on the analysis of 16S ribosomal RNA (rRNA) gene sequences. In asymptomatic, otherwise healthy women, several kinds of vaginal microbiota exist, the majority often dominated by species of *Lactobacillus*, while others comprise a diverse array of anaerobic microorganisms. Bacterial vaginosis is the most common vaginal conditions and is vaguely characterized as the disruption of the equilibrium of the 'normal' vaginal microbiots. A better understanding of 'normal' and 'healthy' vaginal ecosystems that is based on its 'true' function and not simply on its composition would help better define health and further improve disease diagnostics as well as the development of more personalized regimens to promote health and treat diseases.

Keywords

vaginal microbiota; vaginal ecosystem; bacterial vaginosis; health and disease

INTRODUCTION

The microbiota normally associated with the human body have an important influence on human development, physiology, immunity, and nutrition (18; 23; 65; 66; 70; 111). The vast majority of these indigenous microbiota exist in a mutualistic relationship with their human host, while few are opportunistic pathogens that can cause both chronic infections and life-threatening diseases. These microbial communities are believed to constitute the first line of defense against infection by competitively excluding invasive nonindigenous organisms that cause diseases. Despite their importance, surprisingly little is known about how these communities differ between individuals in composition and function, but more importantly, how their constituent members interact with each other and the host to form a dynamic ecosystem that responds to environmental disturbances. Major efforts are now underway to better understand the true role of these communities in health and diseases (84).

The human vagina and the bacterial communities that reside therein are an example of this finely balanced mutualistic association. In this relationship, the host provides benefit to the microbial communities in the form of the nutrients needed to support bacterial growth. This is of obvious importance since bacteria are continually shed from the body in vaginal

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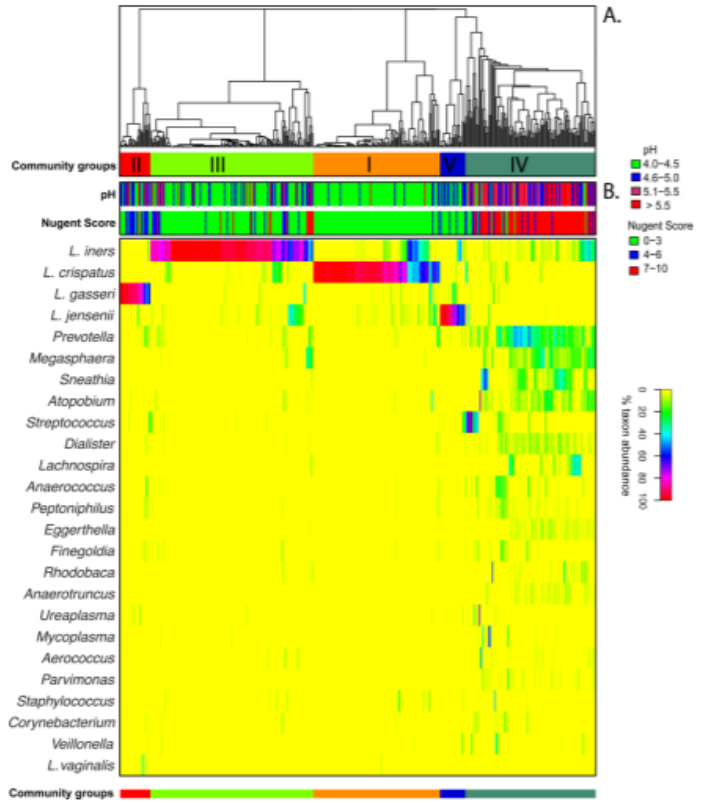
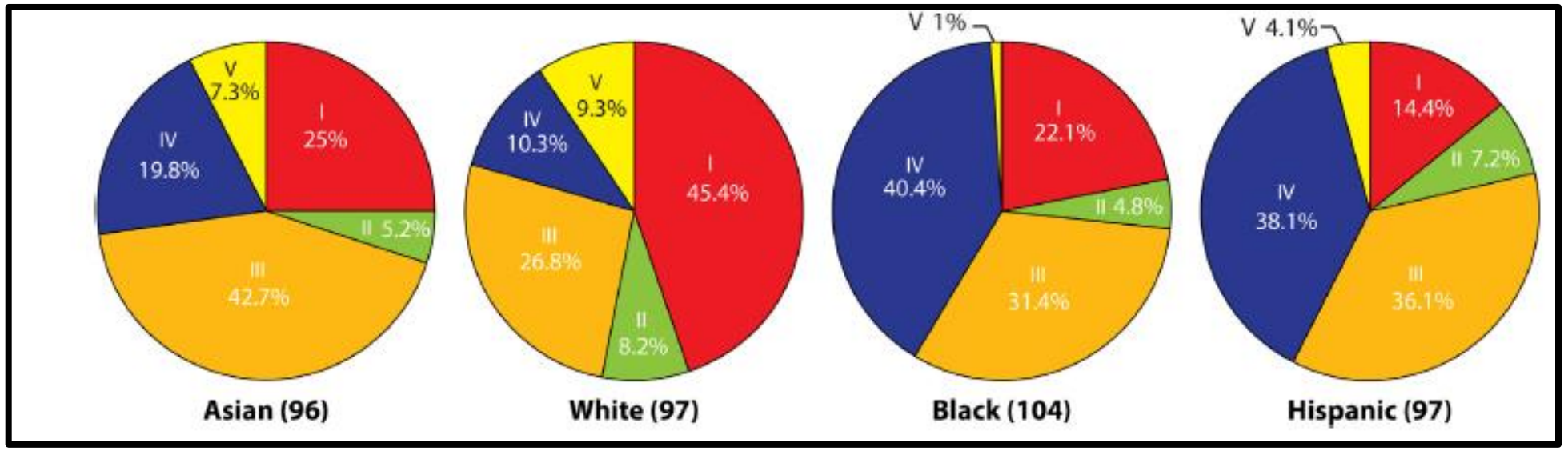


Figure 1.
Heatmap of percentage abundance of microbial taxa found in the vaginal microbial communities of 394 reproductive-age women. (A) Complete linkage clustering of samples based on species composition and abundance in communities defining five community state types (CST I–V). (B) Nugent scores and pH measurements for each of the 394 samples. [Adapted from (86)]



crispatus

gasseri

L. iners

Low lactobacilli

jensenii

Vaccine 32 (2014) 1543–1552

Gautam *et al. BMC Infectious Diseases* (2015) 15:86
DOI 10.1186/s12879-015-0831-1

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Correlates of the molecular vaginal microbiota composition of African women

Raju Gautam[1], Hanneke Borgdorff[2], Vicky Jespers[3], Suzanna C Francis[4], Rita Verhelst[5], Mary Mwaura[6], Sinead Delany-Moretlwe[7], Gilles Ndayisaba[8], Jordan K Kyongo[3], Liselotte Hardy[3], Joris Menten[3], Tania Crucitti[3], Evgeni Tsivtsivadze[9], Frank Schuren[9], Janneke HHM van de Wijgert[1,8,10*] and for the Vaginal Biomarkers Study Group

Prevalence of bacterial vaginosis

WHITE CAUCASIAN
10-20%

AFRO-AMERICAN
30-50%

SEX WORKERS
UP TO 85%

PREGNANT WOMEN
5-26%

Vaccine
Volume 32, Issue 14, 20 March 2014, Pages 1543-1552
Gajer Pawel,Rebecca M.Brotman, Jacqes Ravel

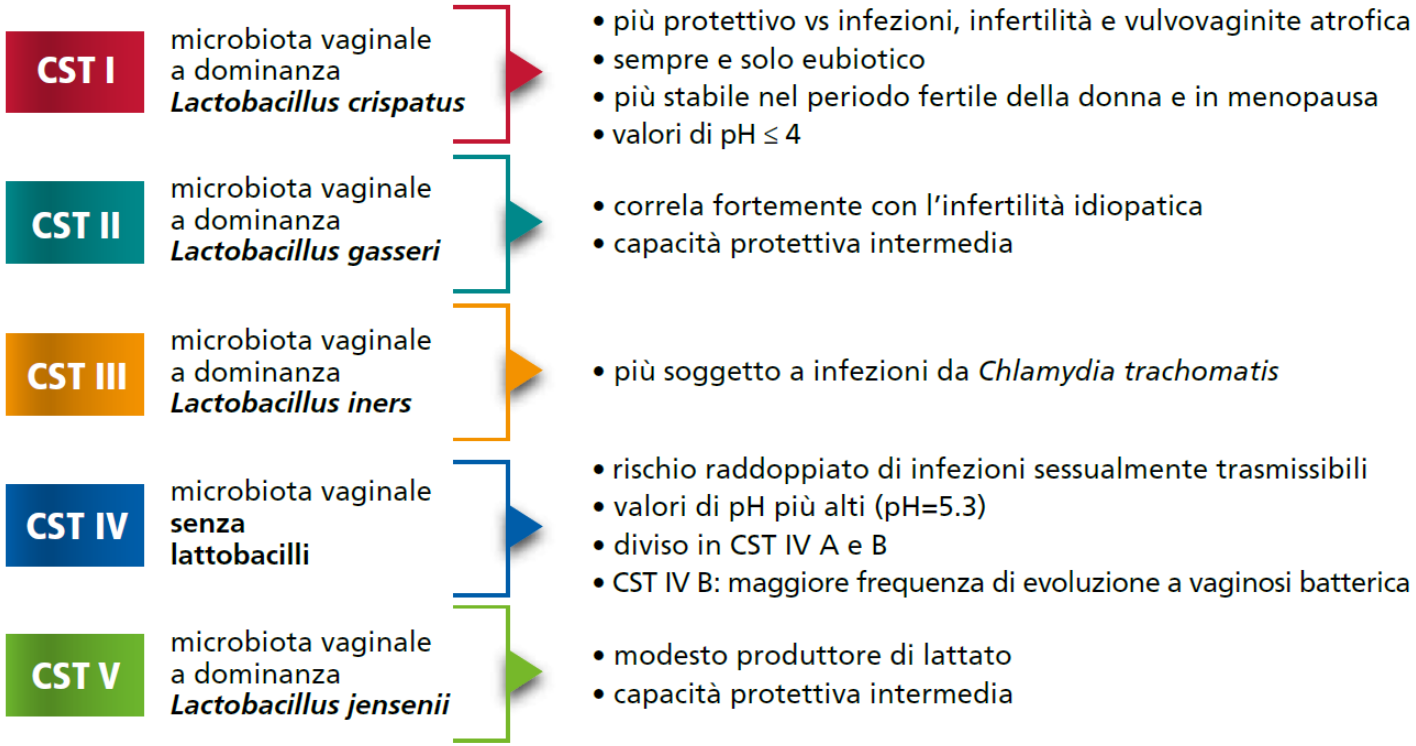
Community state types (CST) in the vaginal microbiota.[a] Vaccine 32 (2014) 1543–1552

CST	Dominant bacterial species
I	*L. crispatus*
II	*L. gasseri*
III	*L. iners*
IV-A[b]	Low-*Lactobacillus*
IV-B[b]	Low-*Lactobacillus*
V	*L. jensenii*

[a] CST IV-A is characterized by various species of anaerobic bacteria including *Anaerococcus*, *Peptoniphilus* and *Prevotella* spp., whereas CST IV-B had higher proportions of bacteria from the genera *Atopobium* and *Megasphaera* among others.

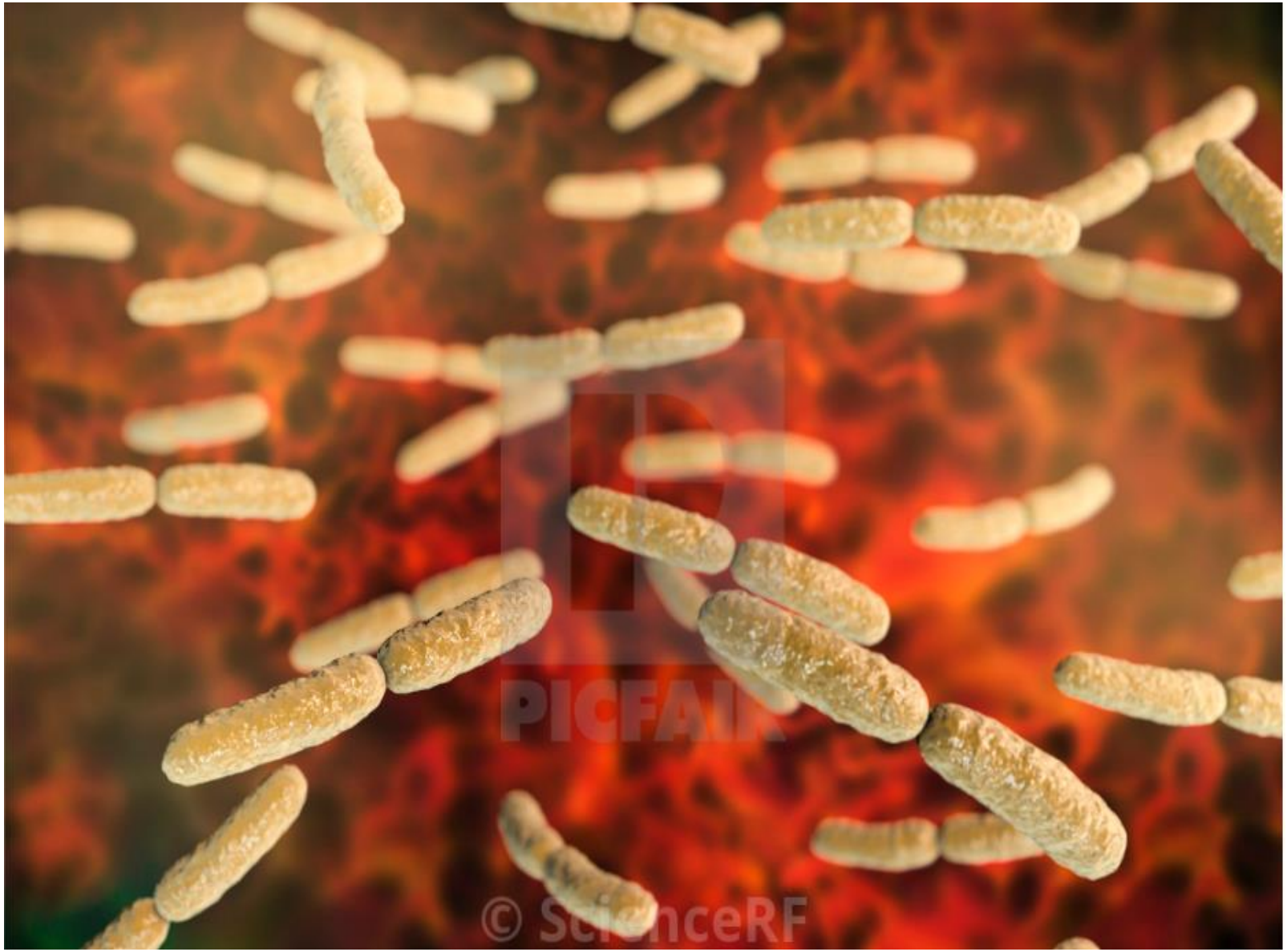
[b] CSTs reflect the clustering of samples based on bacterial composition and abundance. Gajer et al. previously reported on these 6 CSTs among women in Baltimore, MD [54].

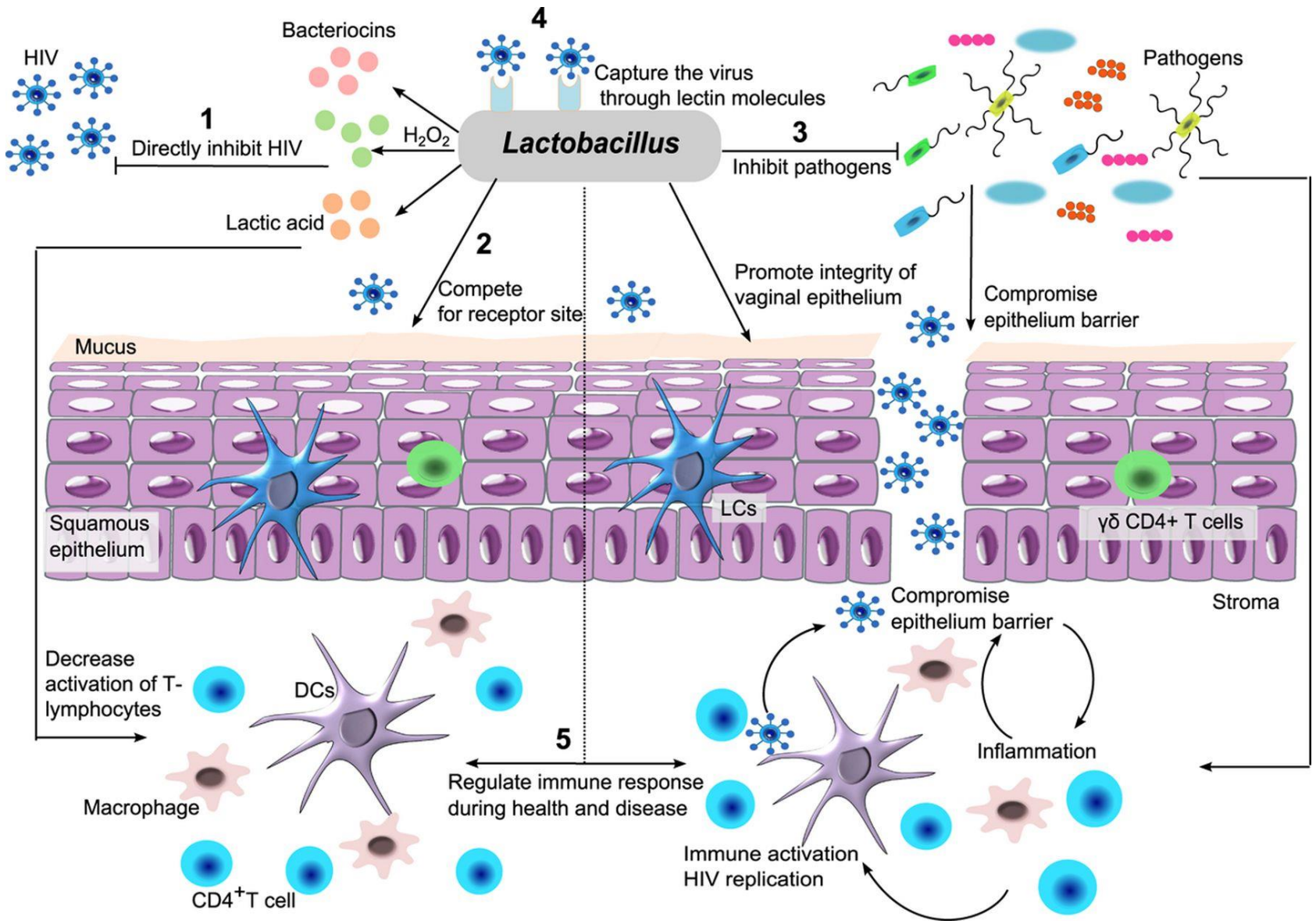
Vaccine
Volume 32, Issue 14, 20 March 2014, Pages 1543-1552
Gajer Pawel, Rebecca M.Brotman, Jacqes Ravel
(modificato)



La dominanza di lattobacilli determina valori più bassi di pH e *Nugent score* [14]

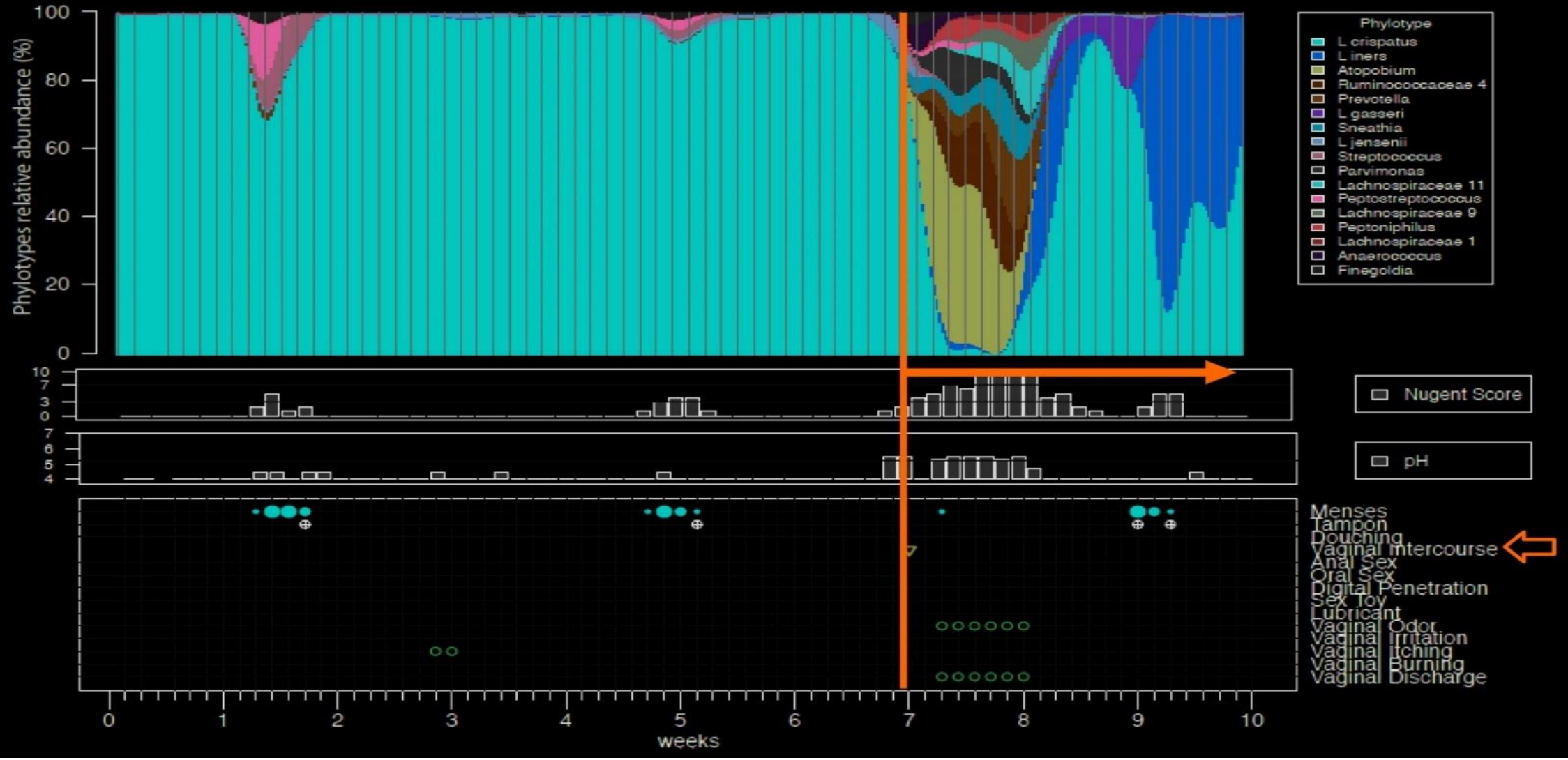
Lactobacillus crispatus (Ph: Firmicutes)



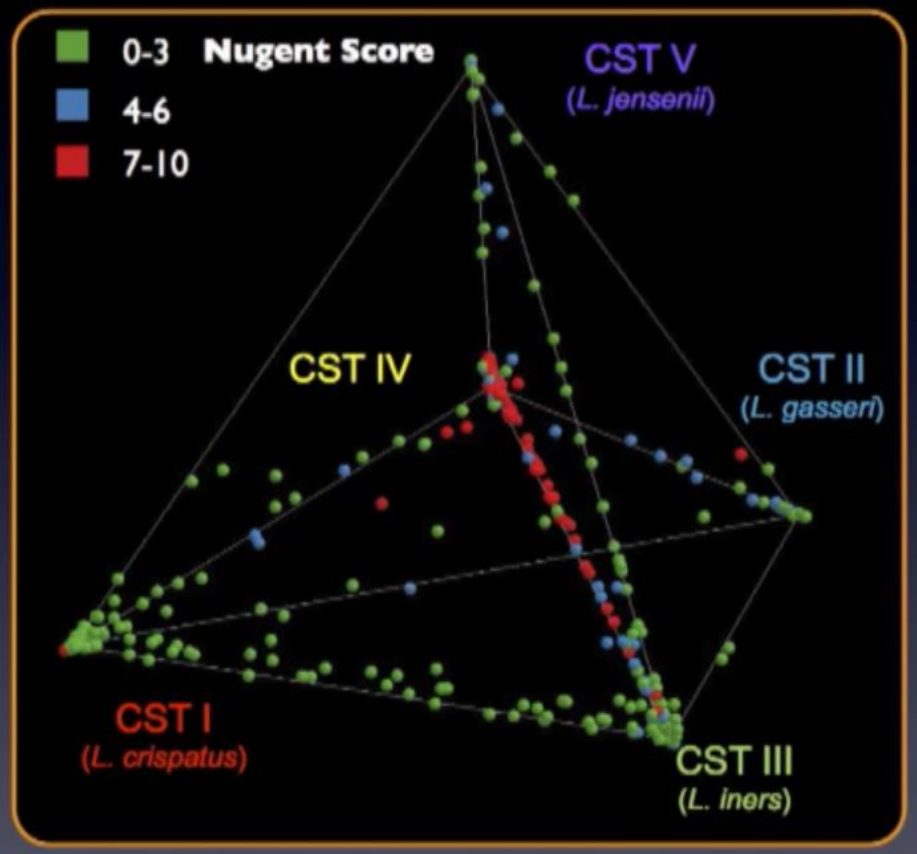

HIV
Bacteriocins
4
Capture the virus
through lectin molecules
Pathogens
1
Directly inhibit HIV
H_2O_2
Lactobacillus
3
Inhibit pathogens
Lactic acid
2
Compete
for receptor site
Promote integrity of
vaginal epithelium
Compromise
epithelium barrier
Mucus
Squamous
epithelium
LCs
γδ CD4+ T cells
Stroma
Compromise
epithelium barrier
Decrease
activation of T-
lymphocytes
DCs
Inflammation
5
Regulate immune response
during health and disease
Macrophage
Immune activation
HIV replication
CD4+T cell

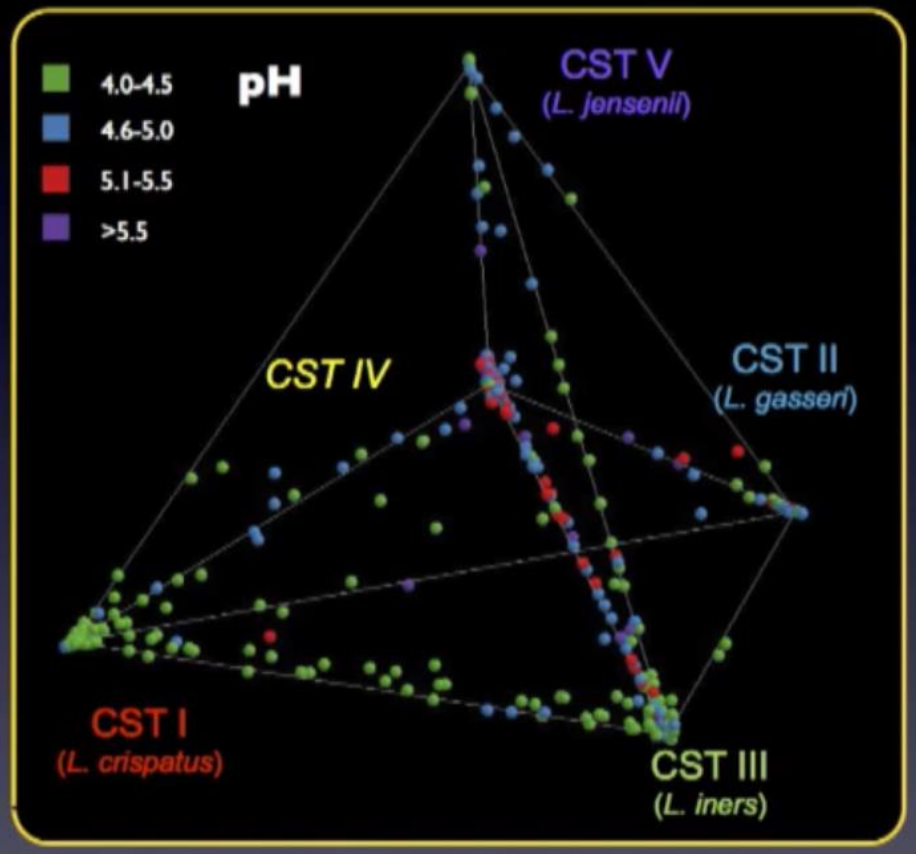
(In)stabilità del microbiota vaginale

Courtesy from Jacques Ravel, University of Maryland

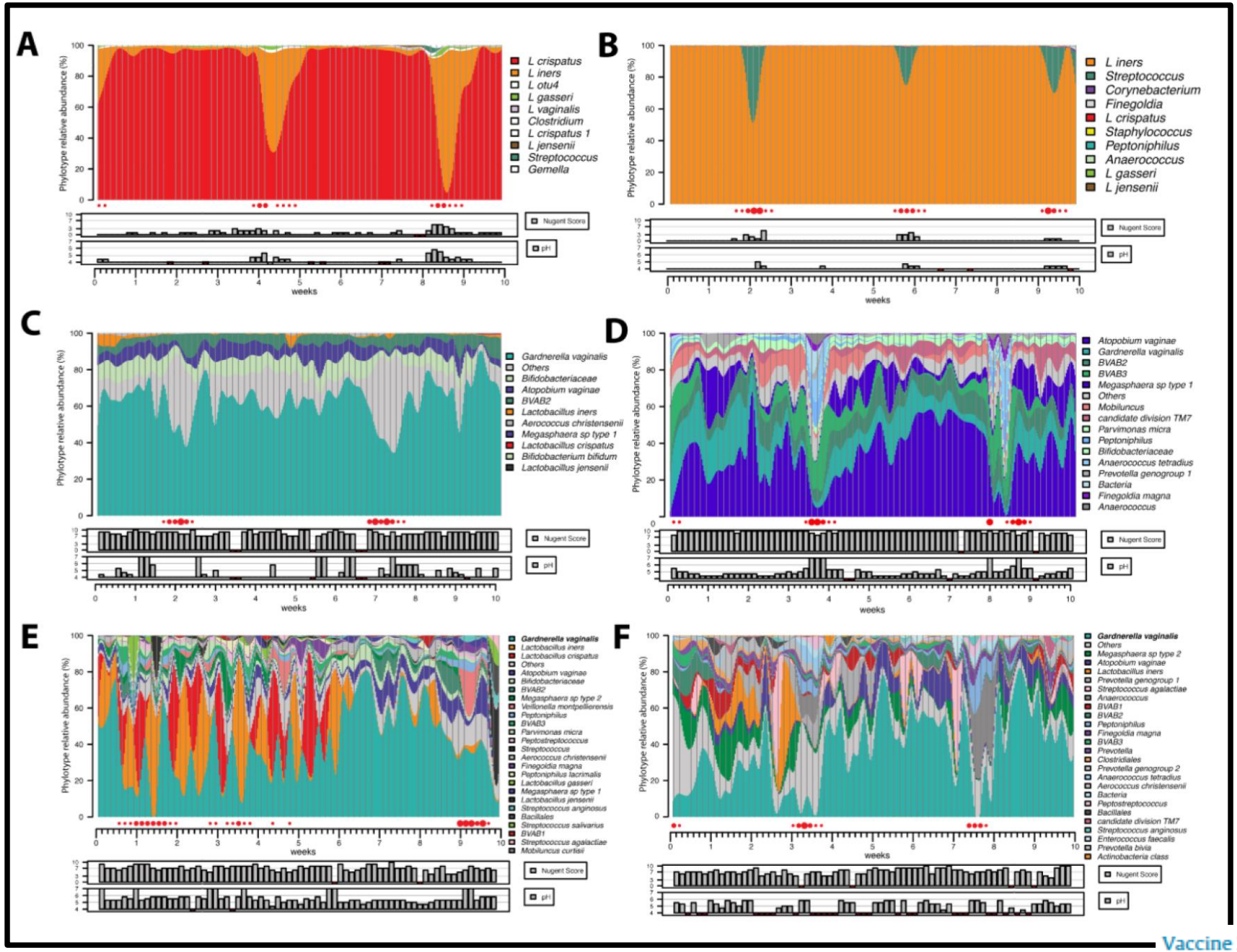


pH, Nugent score, microbial community state





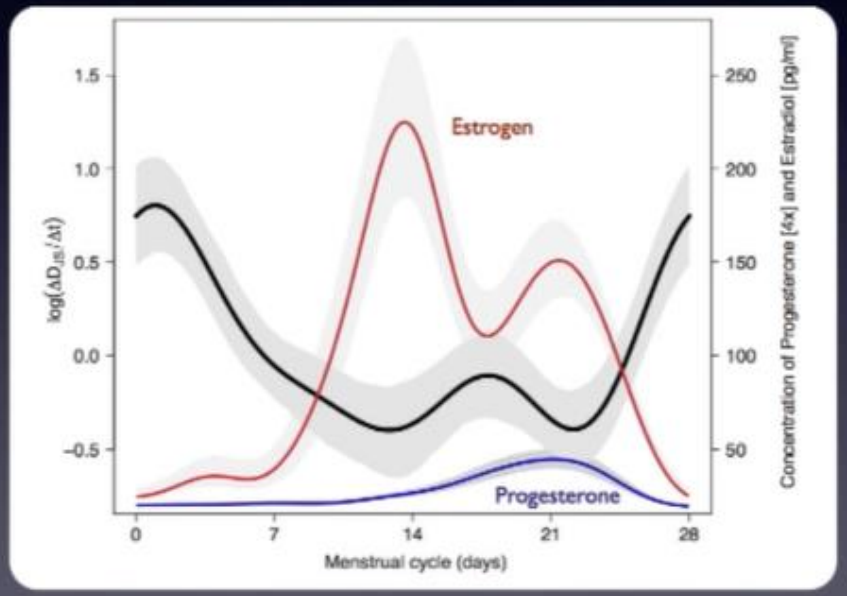
- In these healthy, asymptomatic women, CST IV is associated with higher Nugent scores and higher pH
- How long does this state persist over time? How frequently does the vaginal microbiota of a women is in this state?



Vaccine 32 (2014) 1543–1552

Drivers of unstability

Modeling the dependence of the log of Jensen-Shannon divergence rate of change (estimate of stability) on the menstrual time (normalized time) - Bayesian Markov Chain Monte Carlo methods using linear mixed effect models.



IGS

Gajer et al. The temporal dynamics of the vaginal microbiota. Science Translational Medicine. 2012. 4(132): 132ra52.

CST IV: an healthy state that carry risks?

- At any given time, >25% of women are in a non-lactobacillus dominated state.
  - This state is associated with high Nugent scores and higher pH
  - High Nugent score is associated with increased risk of sexually transmitted infection acquisition and transmission, including HIV, as well as preterm birth
  - These women are "normal" and healthy, but at increased risk of STI or other adverse outcomes
  - Community stability/dynamics (frequency and duration of CST IV) might represent risks to disease

Low stability = low resilience = increased risk

Understand the molecular basis of this association between stability and susceptibility using omics' technologies

www.nature.com/scientificreports

OPEN

Lactobacillus crispatus inhibits the infectivity of *Chlamydia trachomatis* elementary bodies, in vitro study

Received: 02 February 2016
Accepted: 14 June 2016
Published: 29 June 2016

Paola Nardini[1,*], Rogers Alberto Ñahui Palomino[2,*], Carola Parolin[2], Luca Laghi[3], Claudio Foschi[1], Roberto Cevenini[1], Beatrice Vitali[2] & Antonella Marangoni[1]

Lactobacillus species dominate the vaginal microbiota of healthy reproductive-age women and protect the genitourinary tract from the attack of several infectious agents. ***Chlamydia trachomatis***, a leading cause of sexually transmitted disease worldwide, can induce severe sequelae, i.e. pelvic inflammatory disease, infertility and ectopic pregnancy. In the present study we investigated the interference of ***Lactobacillus crispatus***, ***L. gasseri*** and ***L. vaginalis***, known to be dominant species in the vaginal microbiome, with the infection process of ***C. trachomatis***. Lactobacilli exerted a strong inhibitory effect on ***Chlamydia*** infectivity mainly through the action of secreted metabolites in a concentration/pH dependent mode. Short contact times were the most effective in the inhibition, suggesting a protective role of lactobacilli in the early steps of ***Chlamydia*** infection. The best anti-***Chlamydia*** profile was shown by ***L. crispatus*** species. In order to delineate metabolic profiles related to anti-***Chlamydia*** activity, ***Lactobacillus*** supernatants were analysed by ^{1}H-NMR. Production of lactate and acidification of the vaginal environment seemed to be crucial for the activity, in addition to the consumption of the carbonate source represented by glucose. The main conclusion of this study is that high concentrations of ***L. crispatus*** inhibit infectivity of ***C. trachomatis in vitro***.

frontiers in Microbiology

ORIGINAL RESEARCH
published: 04 April 2017
doi: 10.3389/fmicb.2017.00564

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Antimicrobial Compounds Produced by Vaginal *Lactobacillus crispatus* Are Able to Strongly Inhibit *Candida albicans* Growth, Hyphal Formation and Regulate Virulence-related Gene Expressions

Shuai Wang, Qiangyi Wang, Ence Yang, Ling Yan, Tong Li and Hui Zhuang**

a determinant of *C. albicans* pathogenesis. In this study, we investigated the effects of vaginal isolates of *L. crispatus* (seven strains), *L. gasseri* (six strains), and *L. jensenii* (five strains) on growth, hyphal formation and virulence-related genes expression of *C. albicans* ATCC 10231. We found that the *L. crispatus* showed the most significant antimicrobial activities in microplate-based liquid medium assay ($P < 0.05$). All seven cell-free supernatants (CFS) from *L. crispatus* strains reduced the growth of *C. albicans* by >60%. The effects might be due to their productions of some secretory antimicrobial compounds in addition to H_2O_2 and organic acids. Furthermore, each of the CFS of

Sex Transm Infect. 2018 Jan 22. pii: sextrans-2017-053346.

Vaginal microbiota composition and association with prevalent Chlamydia trachomatis infection: a cross-sectional study of young women attending a STI clinic in France.

Tamarelle J et al.

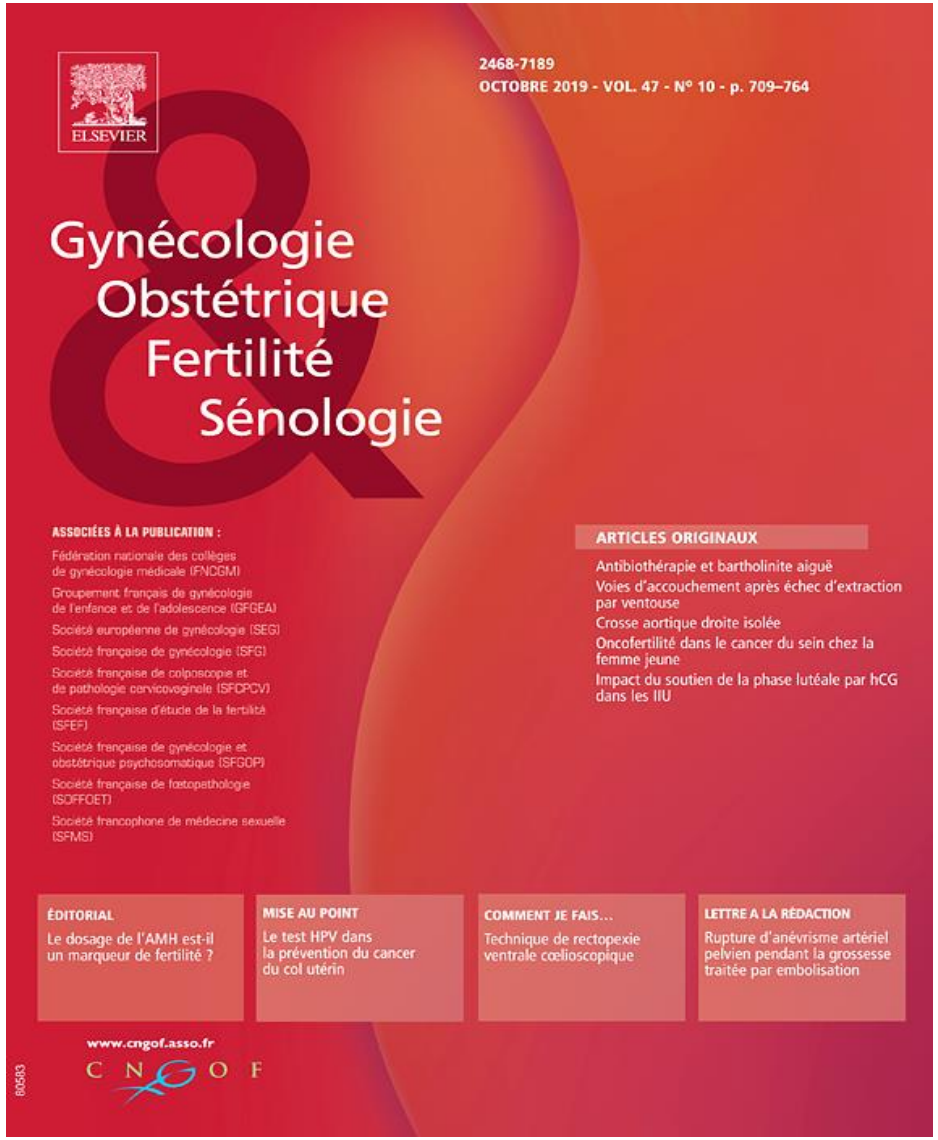
New molecular techniques have allowed describing groups of bacterial communities in the vagina (community state types (CST)) that could play an important role in Chlamydia trachomatis (CT) infection. Our aim was to describe the distribution of CST in a population of young women in France.

A cross-sectional study was carried out in June 2015 among anonymous young women attending a STI clinic in Bordeaux, France. Participants provided a vaginal sample for CT screening and sociodemographic data. CT was diagnosed using the Aptima-combo 2 transcription-mediated-amplification assay. Vaginal microbiota composition was characterised using 16S rRNA gene amplicon sequencing.

Microbiota composition and CT status were available for 132 women. CST dominated by Lactobacillus crispatus (CST-I), L. iners (CST-III) and a diversity of anaerobes (CST-IV) represented 37.1%, 38.6% and 22.0% of the sample, respectively. Twenty-one out of 132 women were CT positive. **Proportions of CT-positive women were higher for samples belonging to CST-III (21.6%) than to CST-I (8.2%) with CST-IV (17.2%).** Five CST were found in 132 young women from a STI clinic in France. These CSTs were not significantly associated with CT but higher proportions of CT-positive women were found in CST-III and CST-IV, consistent with a previous study in the Netherlands. Though our study lacked statistical power and was cross-sectional, it is a necessary first step to understand the structure of the vaginal microbiota in French women with or without infection before performing in-depth longitudinal studies.

C. Cazanave, B. de Barbeyrac,
Les infections génitales hautes : diagnostic microbiologique. RPC infections génitales hautes CNGOF et SPILF,
Gynécologie Obstétrique Fertilité & Sénologie ,
Volume 47, Issue 5,
MAY 2019,
Pages 409-417,

- PIDs also occur in situations that decrease the effectiveness of the cervix microbiological lock, such as bacterial vaginosis, allowing facultative vaginal bacteria such as *Escherichia coli*, *Streptococcus agalactiae* and anaerobes to ascend to the uterine cavity. Nevertheless, participation of the diverse bacteria of the vaginal microbiota, in particular anaerobes, and the polymicrobial character of PIDs are still differently appreciated.



© 2018. Published by The Company of Biologists Ltd | Disease Models & Mechanisms (2018) 11, dmm035147. doi:10.1242/dmm.035147

REVIEW

The relationship between sex hormones, the vaginal microbiome and immunity in HIV-1 susceptibility in women

Jocelyn M. Wessels[1,2], Allison M. Felker[1,2], Haley A. Dupont[1,2] and Charu Kaushic[1,2,*]

ABSTRACT

The role of sex hormones in regulating immune responses in the female genital tract has been recognized for decades. More recently, it has become increasingly clear that sex hormones regulate susceptibility to sexually transmitted infections through direct and indirect mechanisms involving inflammation and immune responses. The reproductive cycle can influence simian/human immunodeficiency virus (SHIV) infections in primates and HIV-1 infection in *ex vivo* cervical tissues from women. Exogenous hormones, such as those found in hormonal contraceptives, have come under intense scrutiny because of the increased susceptibility to sexually transmitted infections seen in women using medroxyprogesterone acetate, a synthetic progestin-based contraceptive. Recent meta-analyses concluded that medroxyprogesterone acetate enhanced HIV-1 susceptibility in women by 40%. In contrast, estradiol-containing hormonal contraceptives were not associated with increased susceptibility and some studies reported a protective effect of estrogen on HIV/SIV infection, although the underlying mechanisms remain incompletely understood. Recent studies describe a key role for the vaginal microbiota in determining susceptibility to sexually transmitted infections, including HIV-1. While *Lactobacillus* spp.-dominated vaginal microbiota is associated with decreased susceptibility, complex microbiota, such as those seen in bacterial vaginosis, correlates with increased susceptibility to HIV-1. Interestingly, sex hormones are inherently linked to microbiota regulation in the vaginal tract. Estrogen has been postulated to play a key role in establishing a *Lactobacillus*-dominated microenvironment, whereas medroxyprogesterone acetate is linked to hypo-estrogenic effects. The aim of this Review is to contribute to a better understanding of the sex-hormone–microbiome–immunity axis, which can provide key information on the determinants of HIV-1 susceptibility in the female genital tract and, consequently, inform HIV-1 prevention strategies.

KEY WORDS: Vaginal microbiota, T cells, DMPA, Inflammation

Introduction

Clinical and experimental evidence indicates that many sexually transmitted infections (STIs) are more prevalent in women than men (Kaushic et al., 2011). The probability of human immunodeficiency virus (HIV) transmission via the female genital tract (FGT) is approximately 1.5- to 5-times greater than via the male genital tract (1 in 2000 to 1 in 200 in females versus 1 in 3000 to 1 in 700 in males) (Hladik and McElrath, 2008). There are both socio-economic and biological reasons why women may be more susceptible to STIs, including HIV-1, than men. The biological factors that could influence the outcome of pathogen exposure in the FGT include its large surface area, the alterations in physiology of reproductive tract tissues during different phases of the menstrual cycle, the influence of sex hormones on mucosal immune defense, the use of hormonal contraceptives and the effect of the indigenous microbiota (see Box 1 for a glossary of terms). In this Review, we highlight the mechanisms by which sex steroid hormones, including hormonal contraceptives, might impact the risk of HIV-1 susceptibility in women. This is an important and timely topic, given that approximately 40% of HIV-1 infections occur in the FGT and that women using the progestin-based injectable contraceptive depot-medroxyprogesterone acetate (DMPA) are 40% more likely to acquire HIV-1 than women not using hormonal contraceptives (Polis et al., 2016). The relevance of this area to public health is emphasized by the fact that more than 8 million women in sub-Saharan Africa, where HIV-1 is endemic, use DMPA as their main form of contraception (Ross and Agwanda, 2012).

The female genital tract

The lower FGT, the vaginal tract and ectocervix (Box 1), is lined with epithelial cells covered by mucus and colonized by bacteria. It is the first location encountered by HIV-1 during heterosexual intercourse with an infected male partner. The lower FGT provides a protective physical and immunological mucosal barrier. Acting as a structural support beneath the epithelium is a dense layer of stromal fibroblasts, in which a diverse population of leukocytes reside (Wira et al., 2005). As HIV-1 preferentially infects $CD4^+$ leukocytes [T cells, macrophages and dendritic cells (DCs)] residing in the stroma, the vaginal mucus and epithelial barrier serve in part to impede viral access to target cells (Pope and Haase, 2003). In order for HIV-1 transmission to occur, infectious virions must transverse the protective physical and immunological barriers of the FGT and infect target cells located in the stroma. While the exact mechanisms by which HIV-1 accesses target cells remain incompletely understood, this Review will focus on several factors known to influence HIV-1 susceptibility and acquisition in the FGT.

The lower FGT is lined with multi-layered squamous epithelial cells, and tight junctions linking these cells are mainly restricted to its basal layers. The epithelium in the lower FGT undergoes continuous differentiation, resulting in a mitotically active basal layer and a terminally differentiated superficial layer comprising cornified epithelial cells, which aid in preventing infection by certain pathogens, including HIV-1 (Anderson et al., 2014). Aside from acting as a physical barrier, the vaginal epithelial cells also secrete mucins (Box 1) into the vaginal lumen. These form a

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C.K., 0000-0002-7088-2569

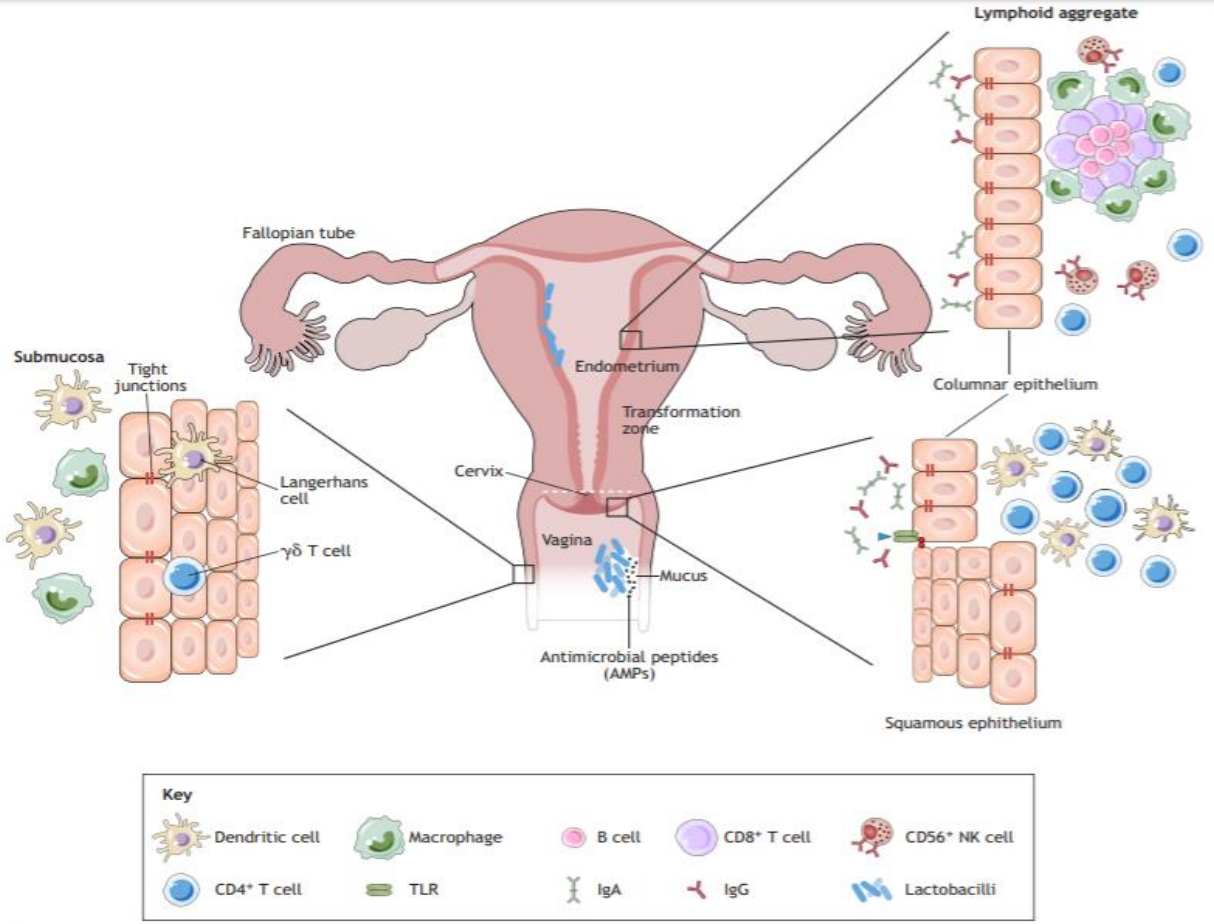
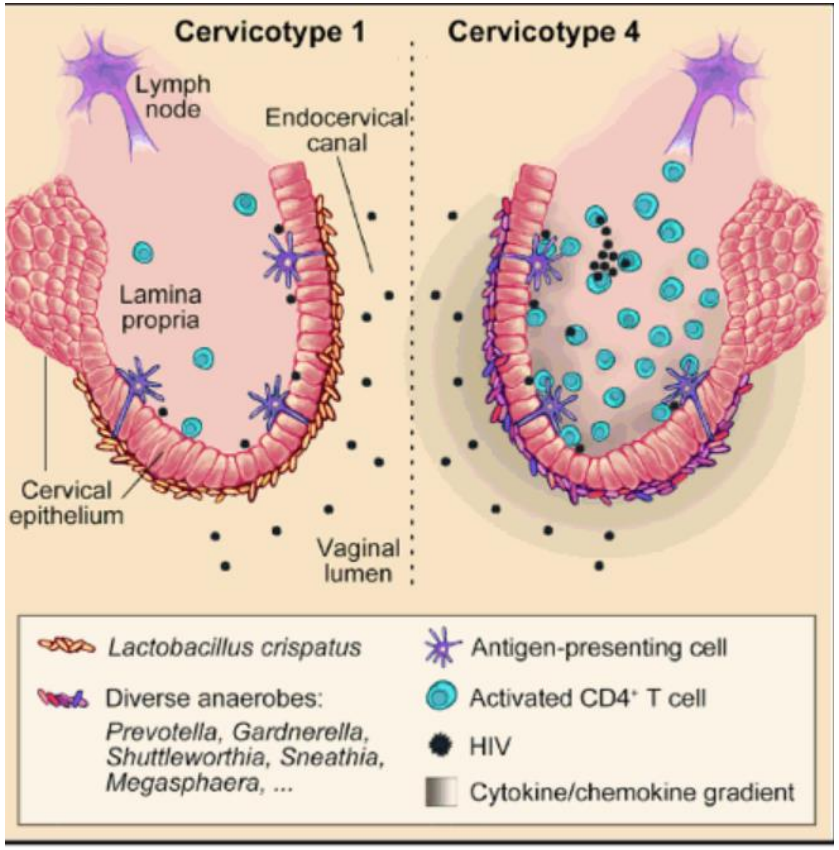


Fig. 1. Anatomy and immunological components of the female genital tract. The female genital tract (FGT) can be separated into the upper (ovary, fallopian tube, uterus/endometrium and endocervix) and lower (ectocervix and vagina) tract. The vaginal epithelium has many innate immune protection mechanisms, such as tight junctions, antimicrobial peptides (AMPs) and mucus, in order to neutralize, trap and prevent entry of potential pathogens. The vaginal lumen is colonized by commensal bacteria, mainly lactobacilli, which help to maintain a low pH. Furthermore, immune cells such as γδ T cells, dendritic cells (DCs) and macrophages are present beneath and between the vaginal epithelial cell layer to survey the local environment for danger. The abrupt transition from keratinized squamous epithelial cells of the ectocervix to single columnar epithelial cells of the endocervix represents the transformation zone; this site has an abundance of HIV-1 target cells and has been proposed to be one of the major sites for infections. The presence of lymphoid aggregates in the endometrial tissue suggests that this is an inductive site for cell-mediated immunity. Lymphoid aggregates found beneath the endometrium are composed of B cells in the inner core surrounded by $CD8^+$ $CD4^-$ T cells and an outer layer of macrophages. A scatter of $CD56^+$ natural killer (NK) cells and $CD4^+$ T cells could be found in between lymphoid aggregates. It was originally believed that the upper FGT was sterile; however, like the vaginal tract, the upper FGT is colonized by bacteria, including lactobacilli. Figure modified and reprinted with permission from Nguyen et al. (2014). TLR, Toll-like receptor.

Vaginosi batterica e Virus (HIV)



Interleukin-6, interleukin-1β, and tumor necrosis factor α in menstrual effluents as biomarkers of chronic endometritis

Cosimo Tortorella, M.D.,[a] Giuseppina Piazzolla, M.D.,[a] Maria Matteo, M.D.,[b] Vincenzo Pinto, M.D.,[b] Raffaele Tinelli, M.D.,[b] Carlo Sabba, M.D.,[a] Margherita Fanelli,[a] and Ettore Cicinelli, M.D.[b]

[a] Dipartimento Interdisciplinare di Medicina and [b] Dipartimento di Scienze Biomediche ed Oncologia Umana, University of Bari, Bari, Italy

Objective: To assess the relationship between chronic endometritis (CE) and proinflammatory cytokine levels in menstrual effluents and to develop a simple noninvasive test for screening CE.
Design: Case-control study.
Setting: Academic center.
Patient(s): Sixty-four women referred to our center for infertility.
Intervention(s): Office hysteroscopy; endometrial biopsy; collection of menstrual blood at subsequent cycle.
Main Outcome Measure(s): Interleukin (IL) 6, IL-1β, and tumor necrosis factor (TNF) α concentrations in menstrual effluents.
Result(s): Thirty-six out of 64 infertile women had histologically proven CE. The remaining 28 women were included as controls. IL-6, IL-1β, and TNF-α levels were markedly higher in menstrual effluents of women with CE compared with control subjects. Receiver operating characteristic curve analysis revealed a good CE screening capacity for all of the cytokines. The combined evaluation of either IL-6/TNF-α or IL-6/IL-1β increased the diagnostic capacity of the test, which reached a 100% sensitivity and a negative predictive value of 100 when at least one cytokine was found to exceed its cutoff value; it also reached a 100% specificity and a positive predictive value of 100 in cases of positivity of both cytokines. Logistic regression analysis confirmed the IL-6/TNF-α–based model as a significant predictor of CE.
Conclusion(s): Proinflammatory cytokine levels are increased in menstrual effluents of women with CE. A test dosing IL-6 and TNF-α seems to have a high screening capacity for CE. (Fertil Steril® 2014;101:242–7. ©2014 by American Society for Reproductive Medicine.)
Key Words: Chronic endometritis, menstrual effluents, cytokines, IL-6, IL-1β, TNF-α

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Chronic endometritis (CE) is a chronic inflammation of the endometrial lining. It is a poorly investigated disorder whose clinical impact, diagnosis, and therapy have not yet been well defined. Clinically, CE is frequently asymptomatic or accompanied by only mild disturbances. Nevertheless, it may account for dysfunctional uterine bleeding (DUB), pelvic pain, and/or reproductive failure [1]. With particular reference to this last point, it is worth mentioning that CE was diagnosed in 9.3% of patients with recurrent miscarriages (in 12.9% of patients with miscarriages of unknown etiology) [2] and in 30.3% of patients with repeated implantation failure after IVF-ET [3].

Histologic examination is considered to be the criterion standard for the diagnosis of CE, with plasma cells found in endometrial stroma being the hallmark of the disorder. The presence of lymphocytes, neutrophils, histiocytes, and eosinophils, on the other hand, is not diagnostic for CE, because they are normal components of the endometrial stroma, especially shortly before menses [1, 4].

We have previously demonstrated that fluid office hysteroscopy is a reliable and useful technique for

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C.T. has nothing to disclose. G.P. has nothing to disclose. M.M. has nothing to disclose. V.P. has nothing to disclose. R.T. has nothing to disclose. C.S. has nothing to disclose. M.F. has nothing to disclose. E.C. has nothing to disclose.
Reprint requests: Ettore Cicinelli, M.D., Section of Obstetrics and Gynaecology, Department of Biomedical Science and Human Oncology, University of Bari, Policlinico, Piazza Giulio Cesare 11, 70124 Bari, Italy (E-mail: ettore.cicinelli@uniba.it).

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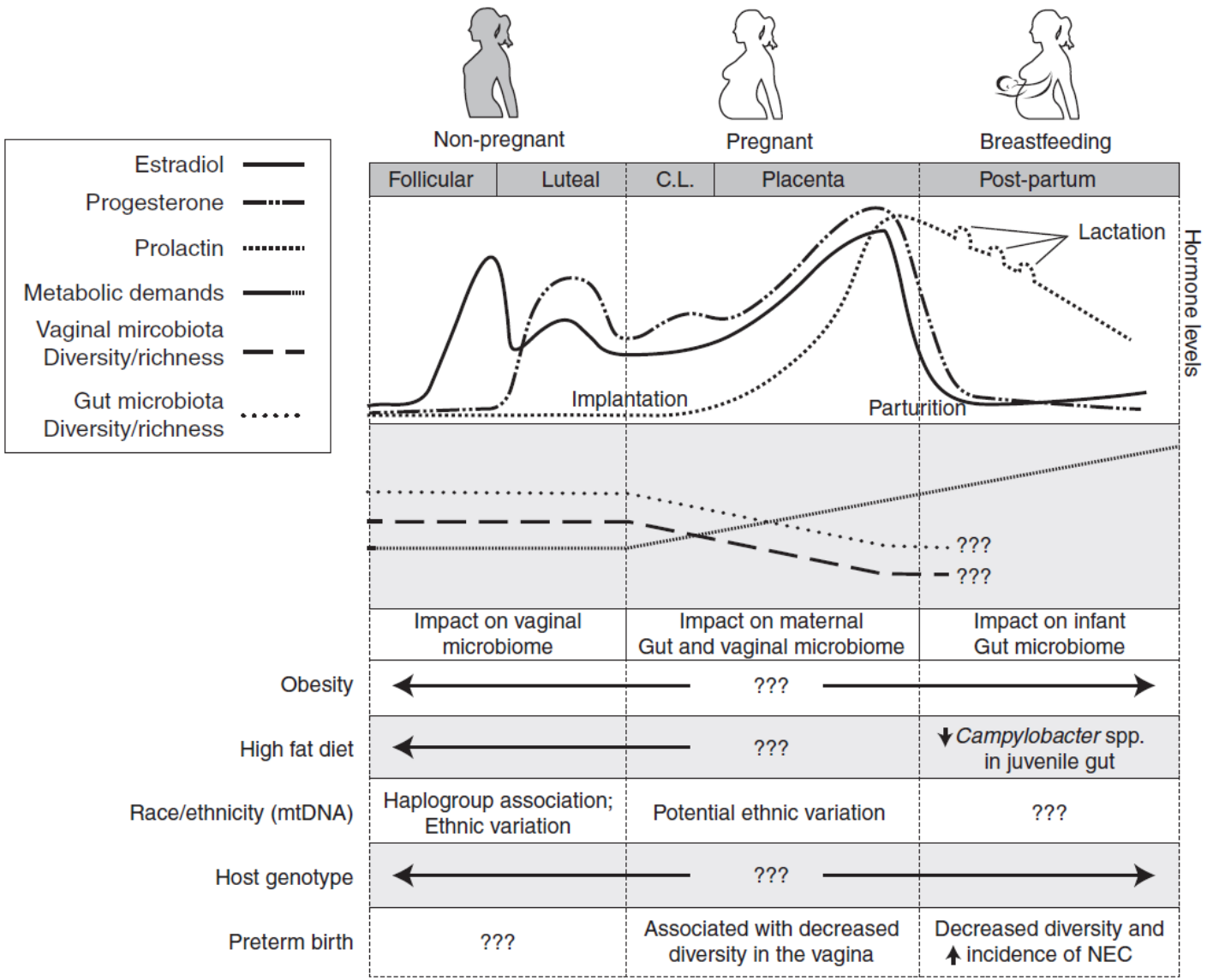
Review

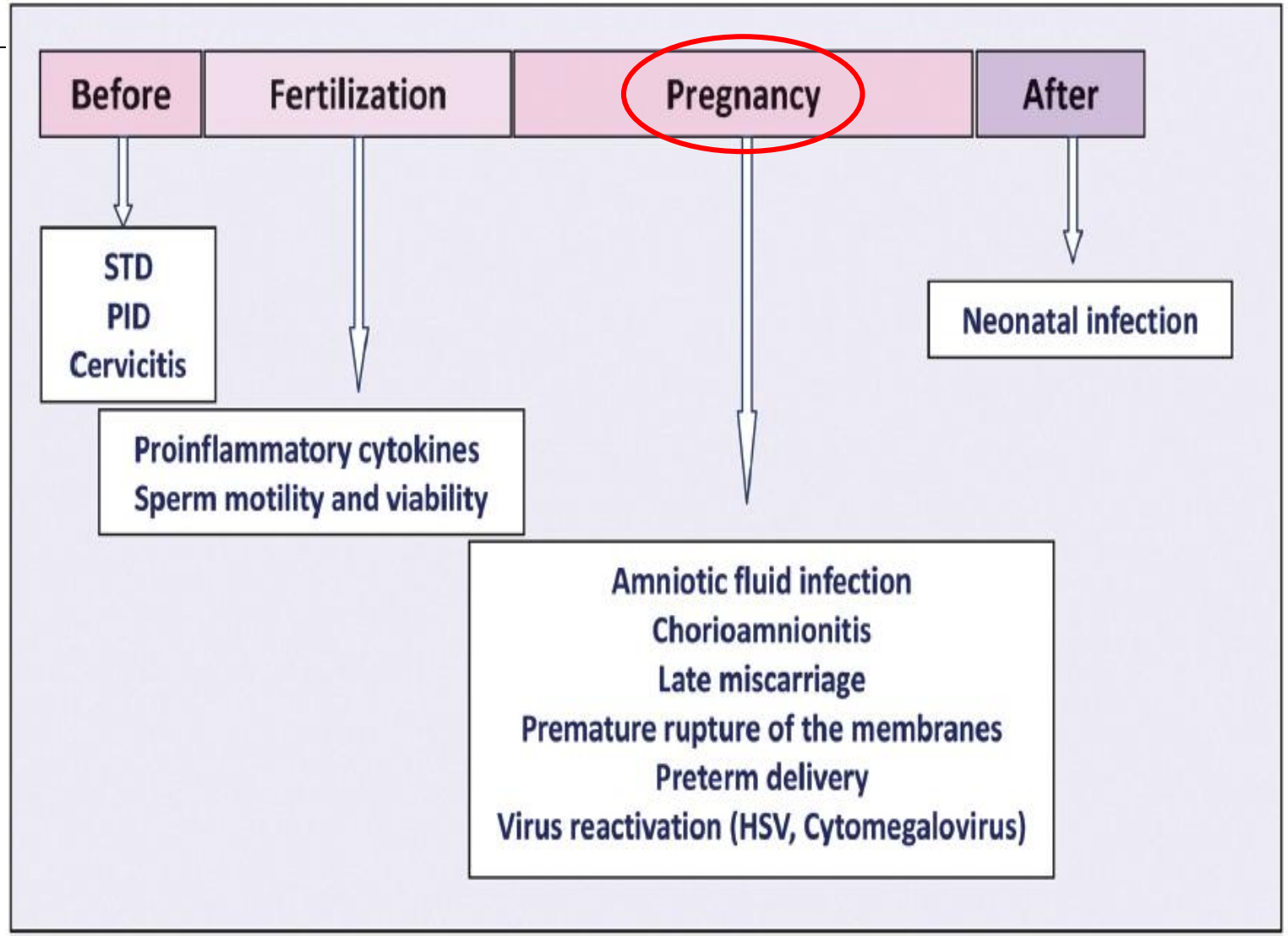
Endocrine, paracrine, and autocrine placental mediators in labor

Zoe Iliodromiti,[1] Nikolaos Antonakopoulos,[2] Stavros Sifakis,[3] Panagiotis Tsikouras,[4] Angelos Daniilidis,[5] Kostantinos Dafopoulos,[6] Dimitrios Botsis,[1] Nikolaos Vrachnis[1]

Bacterial toxins like LPS, originating in microorganisms in uterine or extrauterine tissues, may act on the macrophage-like decidua to initiate a series of events that culminate in preterm labor, possibly together with premature rupture of the fetal membranes. Evidence in support of this hypothesis is that more than 40 years ago it was shown that the administration of LPS to pregnant animals caused abortion or premature parturition. Moreover, in LPS-treated animals, abortion or preterm delivery is associated with decidual hemorrhage and necrosis. Finally, LPS acts on monocytes and macrophages to instigate the production of prostaglandins, TNF-α, and IL-1.[23]


Non-pregnant
Pregnant
Breastfeeding
Estradiol
Progesterone
Prolactin
Metabolic demands
Vaginal mircobiota Diversity/richness
Gut microbiota Diversity/richness
Follicular
Luteal
C.L.
Placenta
Post-partum
Lactation
Implantation
Parturition
Hormone levels
???
???
Impact on vaginal microbiome
Impact on maternal Gut and vaginal microbiome
Impact on infant Gut microbiome
Obesity
???
High fat diet
???
↓Campylobacter spp. in juvenile gut
Race/ethnicity (mtDNA)
Haplogroup association; Ethnic variation
Potential ethnic variation
???
Host genotype
???
Preterm birth
???
Associated with decreased diversity in the vagina
Decreased diversity and ↑ incidence of NEC

Consequences of Bacterial Vaginosis

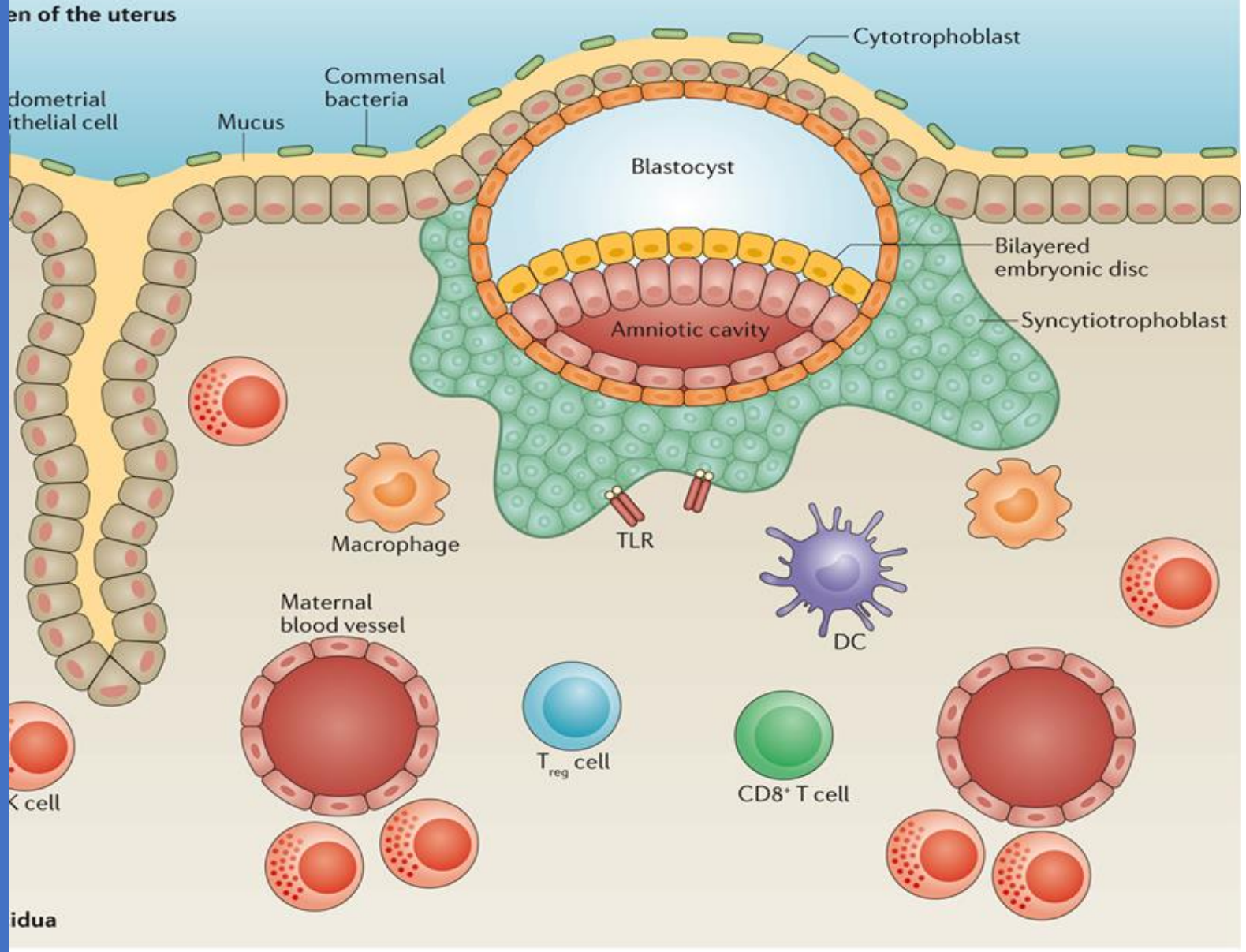


REVIEWS

The unique immunological and microbial aspects of pregnancy

Gil Mor, Paulomi Aldo and Ayesha B. Alvero

Abstract | The comparison of the immunological state of pregnancy to an immunosuppressed host–graft model continues to lead research and clinical practice to ill-defined approaches. This Review discusses recent evidence that supports the idea that immunological responses at the receptive maternal–fetal interface are not simply suppressed but are instead highly dynamic. We discuss the crucial role of trophoblast cells in shaping not only the way in which immune cells respond to the invading blastocyst but also how they collectively react to external stimuli. We also discuss the role of the microbiota in promoting a tolerogenic maternal immune system and highlight how subclinical viral infections can disrupt this status quo, leading to pregnancy complications.



Nature Reviews | Immunology

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American Journal of Obstetrics and Gynecology
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Il microbioma della membrana placentare è alterato tra i soggetti con nascita pretermine spontanea con e senza corioamnionite

Prince Amanda PhD, et alii
Department of Obstetrics & Gynecology, Division of Maternal-Fetal Medicine, Baylor College of Medicine, Houston, TX

- Preterm birth (PTB) is a leading cause of neonatal morbidity and mortality and is not uncommonly associated with chorioamnionitis. We recently have demonstrated that the placenta harbors a unique microbiome with similar flora to the oral community. We also have shown an association of these placental microbiota with PTB, history of antenatal infection, and excess maternal weight gain. On the basis of these previous observations, we hypothesized that the placental membranes would retain a microbiome community that would vary in association with preterm birth and chorioamnionitis.

ARTICLES
https://doi.org/10.1038/s41591-019-0450-2

nature medicine

OPEN

The vaginal microbiome and preterm birth

Jennifer M. Fettweis[1,2,3], Myrna G. Serrano[1,3], J. Paul Brooks[3,4], David J. Edwards[3,5], Philippe H. Girerd[2,3], Hardik I. Parikh[1], Bernice Huang[1], Tom J. Arodz[3,6], Laahirie Edupuganti[1,3], Abigail L. Glascock[7], Jie Xu[3,8,9], Nicole R. Jimenez[1,3], Stephany C. Vivadelli[1,3], Stephen S. Fong[3,10], Nihar U. Sheth[11], Sophonie Jean[1], Vladimir Lee[1,3], Yahya A. Bokhari[5], Ana M. Lara[1], Shreni D. Mistry[1], Robert A. Duckworth III[1], Steven P. Bradley[1], Vishal N. Koparde[11], X. Valentine Orenda[1], Sarah H. Milton[2], Sarah K. Rozycki[12], Andrey V. Matveyev[1], Michelle L. Wright[13,14,15], Snehalata V. Huzurbazar[16], Eugenie M. Jackson[16], Ekaterina Smirnova[17,18], Jonas Korlach[19], Yu-Chih Tsai[19], Molly R. Dickinson[1], Jamie L. Brooks[1], Jennifer I. Drake[1], Donald O. Chaffin[20], Amber L. Sexton[20], Michael G. Gravett[20,21], Craig E. Rubens[20], N. Romesh Wijesooriya[9], Karen D. Hendricks-Muñoz[3,8,9], Kimberly K. Jefferson[1,3], Jerome F. Strauss III[2,3] and Gregory A. Buck[1,3,6*]

The incidence of preterm birth exceeds 10% worldwide. There are significant disparities in the frequency of preterm birth among populations within countries, and women of African ancestry disproportionately bear the burden of risk in the United States. In the present study, we report a community resource that includes 'omics' data from approximately 12,000 samples as part of the integrative Human Microbiome Project. Longitudinal analyses of 16S ribosomal RNA, metagenomic, metatranscriptomic and cytokine profiles from 45 preterm and 90 term birth controls identified harbingers of preterm birth in this cohort of women predominantly of African ancestry. Women who delivered preterm exhibited significantly lower vaginal levels of *Lactobacillus crispatus* and higher levels of BVAB1, *Sneathia amnii*, TM7-H1, a group of *Prevotella* species and nine additional taxa. The first representative genomes of BVAB1 and TM7-H1 are described. Preterm-birth-associated taxa were correlated with proinflammatory cytokines in vaginal fluid. These findings highlight new opportunities for assessment of the risk of preterm birth.

Approximately 15 million preterm births at less than 37 weeks of gestation occur annually worldwide[1]. Preterm birth (PTB) remains the second most common cause of neonatal death across the globe, and the most common cause of infant mortality in middle- and high-income economies[2]. The consequences of PTB persist from early childhood into adolescence and adulthood[3,4]. In the United States, striking population differences with respect to PTB exist, with women of African ancestry having a substantially larger burden of risk. The estimated annual cost of PTB in the United States alone is over US$26.2 billion[5]. Despite these statistics, there remains a paucity of effective strategies for predicting and preventing PTB.

Although maternal and fetal genetics, and gene–environment interactions, clearly play roles in determining the length of gestation, environmental factors, including the microbiome, are the most important contributors to PTB, particularly among women of African ancestry[6]. Microbe-induced inflammation resulting from urinary tract infection, sexually transmitted infections, including trichomoniasis, or bacterial vaginosis is thought to be a cause of PTB[7,8]. Ascension of microbes[7,9] from the lower reproductive tract to the placenta, fetal membranes and uterine cavity, and hematogenous spread of periodontal pathogens from the mouth, have also been invoked to explain the up to 40–50% of preterm births that are associated with microbial etiologies[10,11].

A homogeneous *Lactobacillus*-dominated microbiome has long been considered the hallmark of health in the female reproductive tract. In contrast, a vaginal microbiome with high species diversity, as observed with bacterial vaginosis, has been associated with increased risk for acquisition and transmission of sexually

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Il microbioma vaginale e la nascita pretermine.

Fettweis JM, et alii

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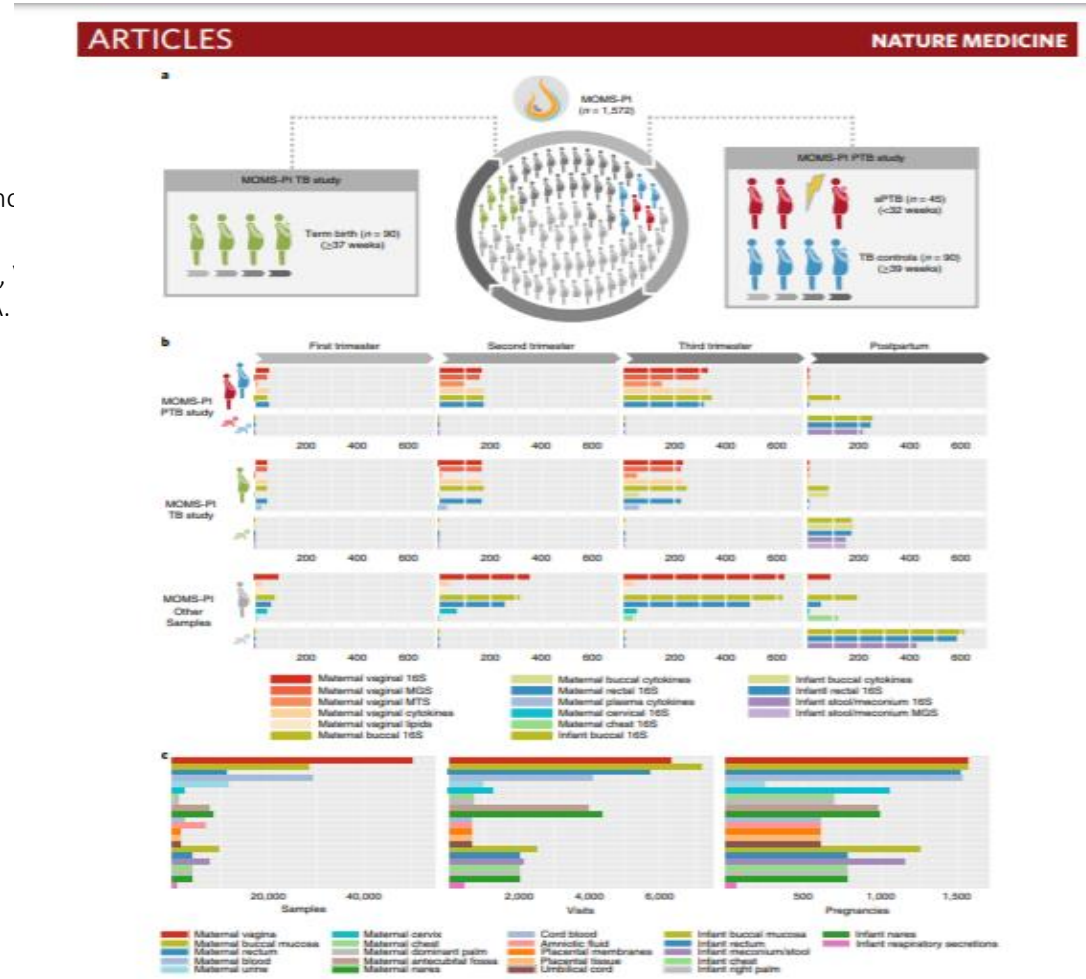

Fig. 1 | MOMS-PI resources. a, An overview of the study designs for the MOMS-PI PTB study (45 spontaneous preterm (sPTB) cases and 90 term controls) and the MOMS-PI TB study (90 women who delivered at term or early term and their neonates). Both cohorts were selected from the phase 1 RAMS Registry cohort ($n = 627$). **b**, Omics data were generated from samples from the MOMS-PI PTB and MOMS-PI TB studies and 384 additional pregnancies from the overall MOMS-PI cohort. Samples from the 12 women who were selected for both the MOMS-PI PTB study and the MOMS-PI TB study are depicted under both studies. Omics data types include 16S rRNA amplicon sequencing, metagenomic sequencing (MGS), metatranscriptomic sequencing (MTS), host cytokine assays and lipidomics. **c**, A total of 206,437 samples were collected at more than 7,000 visits from 1,572 pregnancies in the MOMS-PI study, and are archived in the RAMS Registry.

of 0.723 for samples not used during training. This model, based on microbiome composition data, had 5–7% greater sensitivity and specificity than a model constructed using only clinical variables with a slight reduction in the AUROC curve (that is, 0.723 versus 0.764). A network analysis of these four taxa (Fig. 2c) shows them to be positively correlated with taxa associated with vaginal dysbiosis.

frontiers in Medicine

ORIGINAL RESEARCH
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Vaginal Microbiome Signature Is Associated With Spontaneous Preterm Delivery

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Background: Preterm delivery (PTD) represents an important public health and therapeutic challenge. Despite the reported link between the composition of vaginal microbiome and PTD, previous studies were inconsistent in their conclusions and utilized non-uniform designs. We performed an independent case-control study carried out on the Slovenian population, where we re-evaluated the role of the vaginal microbiome in PTD.

Methods: Vaginal microbiomes of pregnant women who delivered preterm were compared to those delivered at term to examine differences in the microbial richness, diversity, and differential abundance of specific taxa. We obtained vaginal swab samples from 155 Caucasian women who were classified as either term ($\geq 38^{0/7}$ weeks, $n = 107$) or preterm ($\leq 36^{6/7}$ weeks, $n = 48$) in exclusion of any other medical or obstetric conditions. The vaginal microbiomes of these women were characterized by 16S ribosomal RNA (rRNA) gene sequencing of the V3-V4 region on the MiSeq platform.

Results: Women who experienced PTD had a higher microbial richness (Chao1, $P = 0.011$) and alpha diversity (Shannon, $P = 0.00059$) than women with term deliveries. We report that overall vaginal microbial community composition (beta-diversity) was significantly different by delivery gestational age category ($P_{\text{Weighted Unifrac}} < 0.001$). Women who delivered preterm had decreased *Lactobacilli* spp. abundance as well as increased abundance of *Gardnerella* and other bacterial vaginosis (BV) and aerobic vaginitis (AV) associated genera including *Atopobium*, *Sneathia*, *Gemella*, *Megasphaera*, *Dorea*, *Streptococcus*, and *Escherichia/Shigella*.

Conclusions: In the present study, we provide further evidence that vaginal microbiome composition is associated with PTD.

Keywords: preterm delivery, microbiome, next-generation sequencing, 16S rRNA gene, vaginal microbiome, pregnancy

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Microbiome

RESEARCH Open Access

The interaction between vaginal microbiota, cervical length, and vaginal progesterone treatment for preterm birth risk

Lindsay M. Kindinger[1,2,3], Phillip R. Bennett[1,2], Yun S Lee[1], Julian R. Marchesi[4,5,6], Ann Smith[5], Stefano Cacciatore[1], Elaine Holmes[4,6], Jeremy K. Nicholson[4,6], T. G. Teoh[1,3] and David A. MacIntyre[1*]

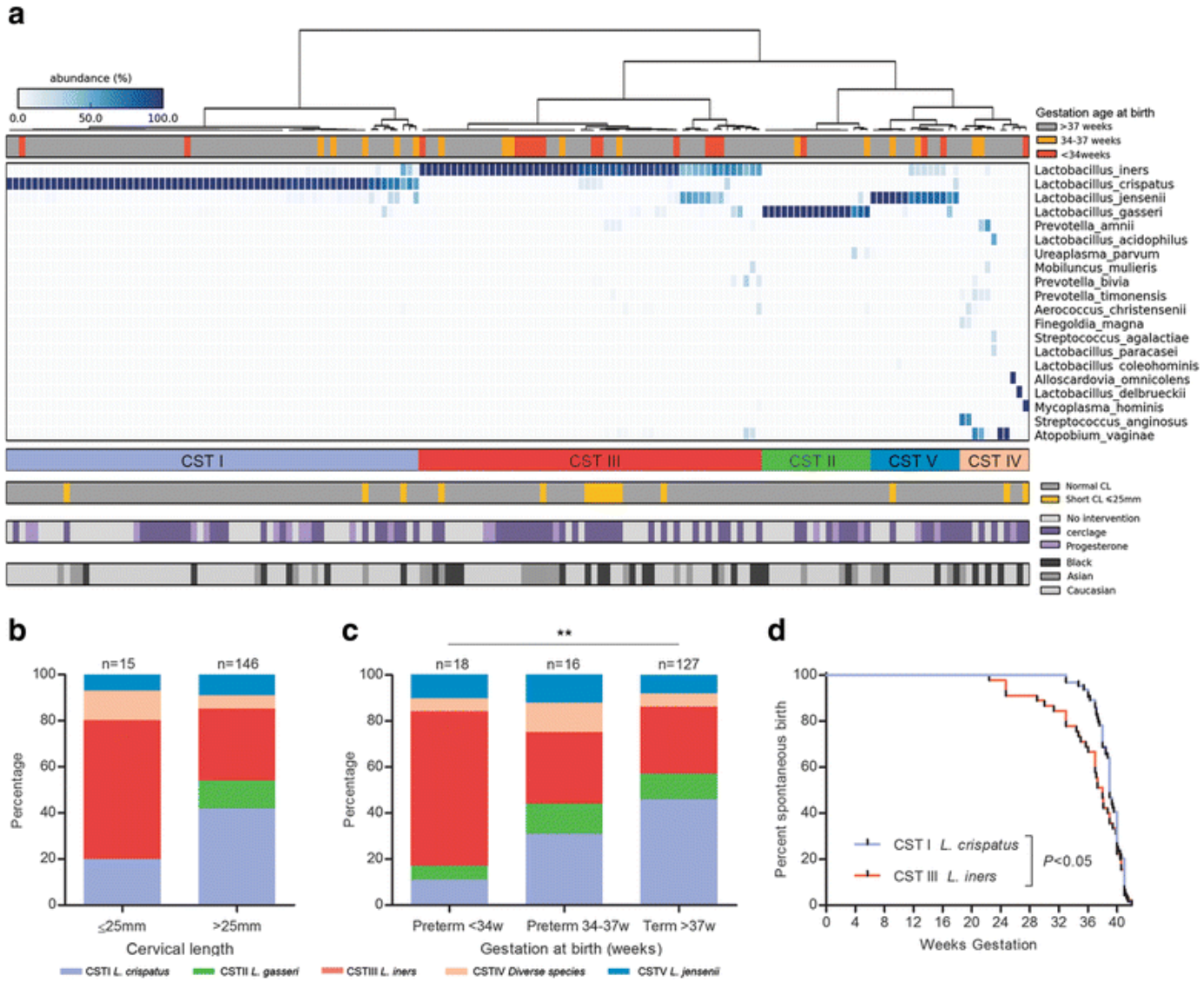
Abstract

Background: Preterm birth is the primary cause of infant death worldwide. A short cervix in the second trimester of pregnancy is a risk factor for preterm birth. In specific patient cohorts, vaginal progesterone reduces this risk. Using 16S rRNA gene sequencing, we undertook a prospective study in women at risk of preterm birth ($n = 161$) to assess (1) the relationship between vaginal microbiota and cervical length in the second trimester and preterm birth risk and (2) the impact of vaginal progesterone on vaginal bacterial communities in women with a short cervix.

Results: *Lactobacillus iners* dominance at 16 weeks of gestation was significantly associated with both a short cervix <25 mm ($n = 15$, $P < 0.05$) and preterm birth $<34^{+0}$ weeks ($n = 18$; $P < 0.01$; 69% PPV). In contrast, *Lactobacillus crispatus* dominance was highly predictive of term birth ($n = 127$, 98% PPV). Cervical shortening and preterm birth were not associated with vaginal dysbiosis. A longitudinal characterization of vaginal microbiota (<18, 22, 28, and 34 weeks) was then undertaken in women receiving vaginal progesterone (400 mg/OD, $n = 25$) versus controls ($n = 42$). Progesterone did not alter vaginal bacterial community structure nor reduce *L. iners*-associated preterm birth (<34 weeks).

Conclusions: *L. iners* dominance of the vaginal microbiota at 16 weeks of gestation is a risk factor for preterm birth, whereas *L. crispatus* dominance is protective against preterm birth. Vaginal progesterone does not appear to impact the pregnancy vaginal microbiota. Patients and clinicians who may be concerned about "infection risk" associated with the use of a vaginal pessary during high-risk pregnancy can be reassured.

MICROBIOMA , (2017) 5-6 the interaction between vaginal microbiota, cervical length, and vaginal progesterone treatment for preterm birth risk



Effect of population-based antenatal screening and treatment of genitourinary tract infections on birth outcomes in Sylhet, Bangladesh (MIST): a cluster-randomised clinical trial

Anne CC Lee, Luke C Mullany, Mohammad Quaiyum, Dipak K Mitra, Alain Labrique, Parul Christian, Parvez Ahmed, Jamal Uddin, Iftekhar Rafiqullah, Sushil DasGupta, Mahmoodur Rahman, Emilia H Koumans, Salahuddin Ahmed, Samir K Saha, Abdullah H Baqui, for the Projahnmo Study Group in Bangladesh

Summary

Background One-third of preterm births are attributed to pregnancy infections. We implemented a community-based intervention to screen and treat maternal genitourinary tract infections, with the aim of reducing the incidence of preterm birth.

Methods We did an unblinded cluster-randomised controlled trial in two subdistricts of Sylhet, Bangladesh. Clusters were defined as the contiguous area served by a single community health worker, and each cluster comprised several contiguous villages, contained roughly 4000 people, and had about 120 births per year. Eligible participants within clusters were all ever-married women and girls of reproductive age (ie, aged 15–49 years) who became pregnant during the study period. Clusters were randomly assigned (1:1) to the intervention or control groups via a restricted randomisation procedure. In both groups, community health workers made home visits to identify pregnant women and girls and provide antenatal and postnatal care. Between 13 and 19 weeks' gestation, participants in the intervention group received home-based screening for abnormal vaginal flora and urinary tract infections. A random 10% of the control group also received the intervention to examine the similarity of infection prevalence between groups. If present, abnormal vaginal flora (ie, Nugent score ≥4 was treated with oral clindamycin (300 mg twice daily for 5 days) and urinary tract infections with cefixime (400 mg once daily for 3 days) or oral nitrofurantoin (100 mg twice daily for 7 days). Both infections were retreated if persistent. The primary outcome was the incidence of preterm livebirths before 37 weeks' gestation among all livebirths. This trial is registered with ClinicalTrials.gov, number NCT01572532. The trial is closed to new participants, with follow-up completed.

Findings Between Jan 2, 2012, and July 28, 2015, 9712 pregnancies were enrolled (4840 in the intervention group, 4391 in the control group, and 481 in the control subsample). 3818 livebirths in the intervention group and 3557 livebirths in the control group were included in the primary analysis. In the intervention group, the prevalence of abnormal vaginal flora was 16·3% (95% CI 15·1–17·6) and that of urinary tract infection was 8·6% (7·7–9·5). The effective coverage of successful treatment in the intervention group was 58% in participants with abnormal vaginal flora (ie, abnormal vaginal flora resolved in 361 [58%] of the 622 participants who initially tested positive), and 71% in those with urinary tract infections (ie, resolution in 224 [71%] of the 317 participants who initially tested positive). Overall, the incidence of preterm livebirths before 37 weeks' gestation did not differ significantly between the intervention and control groups (21·8% *vs* 20·6%; relative risk 1·07 [95% CI 0·91–1·24]).

Interpretation A population-based antenatal screening and treatment programme for genitourinary tract infections did not reduce the incidence of preterm birth in Bangladesh.

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Lancet Glob Health 2019; 7: e148–59

See Comment page e18

Department of Pediatric Newborn Medicine, Brigham and Women's Hospital, Boston, MA, USA (A C Lee MD); International Center for Maternal and Newborn Health (Prof L C Mullany PhD, Prof A H Baqui DrPH), Department of International Health (A Labrique PhD, Prof P Christian PhD), Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; International Center for Diarrheal Diseases—Bangladesh, Center for Reproductive Health, Dhaka, Bangladesh (M Quaiyum MBBS, P Ahmed MBBS, S DasGupta MS, M Rahman MBBS); North South University, Dhaka, Bangladesh (D K Mitra PhD); Independent University, Bangladesh, Dhaka, Bangladesh (J Uddin MBBS); Bill & Melinda Gates Foundation, Seattle, WA, USA (Prof P Christian); Department of Microbiology and Immunology, University of Mississippi Medical Center, Jackson, MS, USA (I Rafiqullah MS); Centers for Disease Control and Prevention, Atlanta, GA, USA (E H Koumans MD); Johns Hopkins University—Bangladesh, Dhaka, Bangladesh (S Ahmed MBBS); and Child Health Research Foundation, Department of Microbiology, Dhaka Shishu Hospital, Dhaka, Bangladesh (Prof S K Saha PhD)

Introduction

Globally, an estimated 14·8 million infants were born preterm (<37 weeks' gestation) in 2014, and preterm birth rates are increasing in many countries.[1] More than 90% of preterm births occur in low-income and middle-income countries (LMICs),[2] where access to, and quality of, antenatal, intrapartum, and postnatal care vary. Complications from preterm birth are now the leading cause of child mortality and account for 1 million neonatal deaths annually.[3] Survivors of preterm birth have increased risk of neurodevelopmental impairment, stunting, and chronic disease.[4,5] Thus, effective strategies

be reported elsewhere). The WHO Global Surveillance of Antimicrobial Resistance reported high rates of resistance in *Escherichia coli* (16–68% resistance to third-generation cephalosporins and 32–64% resistance to fluoroquinolones) in national data from five countries in southeast Asia.[58,59] Safety of antibiotic regimens is a consideration in pregnancy and limits the choice of therapeutic, bactericidal antimicrobials. Antibiotic stewardship and development of effective antimicrobials are crucial priorities to improve the efficacy of treatment of urinary tract infections during pregnancy in LMICs.[59,60]

A Cochrane review[20] of data from 13 trials of bacterial vaginosis (combined n=6491) concluded that treatment of asymptomatic bacterial vaginosis in the general obstetric population did not reduce the risk of preterm birth (pooled RR 0·88 [95% CI 0·71–1·09]). One of the largest studies, the National Institute of Child Health and Human Development's Maternal Fetal Medicine Unit trial,[61] showed that treatment of bacterial vaginosis with metronidazole did not affect preterm delivery in low-risk obstetric populations. Furthermore, mothers with asymptomatic trichomonas who received metronidazole had increased rates of preterm birth compared with those who received placebo.[61] Results from the PREMEVA1 trial[62] published in 2018 showed that treatment of bacterial vaginosis in early pregnancy with oral clindamycin did not reduce rates of late abortion or spontaneous preterm birth.

However, reductions in the incidence of preterm birth were reported in previous trials that targeted abnormal vaginal flora (ie, intermediate flora in addition to bacterial vaginosis). In a pooled analysis in the Cochrane review[20] of two trials[22,23] (combined n=894) that targeted abnormal vaginal flora (ie, intermediate flora and bacterial vaginosis), treatment of abnormal vaginal flora was associated with significant reductions in the frequency of preterm birth (ie, <37 weeks' gestation; RR 0·53 [95% CI 0·34–0·84]).

Unlike in these two trials,[22,23] in which individual metronidazole treatment and only half of mothers remaining non-infected in long-term follow-up.[63–65] We anticipated higher rates of cure with oral clindamycin in our trial, because the drug has good clinical efficacy against intermediate flora, anaerobic species,[66] and persistent bacterial vaginosis[67] (specifically metronidazole-resistant *Gardnerella vaginalis*).[68] The microbial composition of abnormal vaginal flora could differ in the Bangladeshi population compared with that in the UK study populations in which the clinical efficacy of clindamycin was established.[22,69] Abnormal vaginal flora is a heterogeneous, polymicrobial condition, and the vaginal microbiome varies between ethnic groups in the USA and Africa.[70–72] Differences in antibiotic response have also been reported between US and Kenyan women.[73] Furthermore, certain microbiota, including bacterial-vaginosis-associated bacteria-2[74] and *Lactobacillus iners*,[75] are associated with persistent bacterial vaginosis and vaginal inflammation. Study of the vaginal microbiome in our population is needed to identify the specific microbiota associated with persistent abnormal vaginal flora and to target diagnostics and antimicrobial treatment against these species.

Beyond the identification of microbiota associated with abnormal vaginal flora in this population, it is crucial to understand the role of these microbiota in host immune responses to elucidate the pathophysiology of preterm birth.[71] Characterisation of the host inflammatory response to microbiota associated with abnormal vaginal flora may help to clarify why the intervention had no effect in our population. For example, single nucleotide polymorphisms in pro-inflammatory cytokines (eg, tumour necrosis factor α, interleukins 6 and 1β) are associated with preterm birth,[76,77] and several investigators have reported a gene–environment interaction in which bacterial vaginosis could modify the host inflammatory response.[78–80]

Our trial differed in terms of methods and population from previous trials of treatment of abnormal vaginal flora[22,23] and lower genital tract screening,[81] in which

La Resistenza agli antibiotici

- **La resistenza si definisce come lo sviluppo della capacità di un microrganismo di sopravvivere a farmaci che dovrebbero ucciderlo o indebolirlo.**

- **Se un microrganismo diventa resistente a diversi farmaci, trattare l'infezione causata da tale agente può diventare difficile se non impossibile.**

- **I microrganismi resistenti possono essere trasmessi da persona a persona. In questo modo infezioni difficili da trattare possono diffondere con conseguenze serie fino alla morte.**

BIOFILM PATOGENI

Rappresentano comunità strutturate di cellule batteriche spesso di natura diversa anche fungina racchiuse in una matrice polimerica autoprodotta ed adesa ad una superficie inerte o vivente. (Aparna e Brez, J. Infect Dis; 2008(6):526-30.

Nell'ambiente vaginale il biofilm fisiologico è costituito per il 90% da miscele di lattobacilli e per il 10% da batteri saprofiti. (Atassi e Servin, 2010 Microbiol Lett. 304(1):29.38

Le alterazioni dell'equilibrio dell'ecosistema è il presupposto per la attivazione del biofilm patogeno caratterizzato da resistenza alla terapia antibiotica e agli effettori della risposta immunitaria. Swidsinski et al. 2008, Am J. Obst Gynecol.;198(1):97.

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The prediction of preterm delivery: What is new?

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ABSTRACT

Preterm birth, defined as birth occurring prior to 37 weeks gestation, is a serious obstetric problem accounting for 11% of pregnancies worldwide. It is associated with significant neonatal morbidity and mortality. Predictive tests for preterm birth are incredibly important, given the huge personal, economic, and health impacts of preterm birth. They can provide reassurance for women who are unlikely to deliver early, but they are also important for highlighting those women at higher risk of premature delivery so that we can offer prophylactic interventions and help guide antenatal management decisions. Unfortunately, there is unlikely to be a single test for predicting preterm birth, but a combination of tests is likely to improve clinical prediction. This review explores the clinical utility of the currently marketed predictive tests for preterm birth in both singleton and multiple pregnancies, as well as discussing novel predictive tests that may be useful in the future.

1. Introduction

Preterm birth, delivery before 37 weeks gestation, is a major obstetric and global health problem. It is the largest direct cause of mortality in infants aged < 5 years and associated with serious morbidity in the surviving infants [1,2]. Worldwide, 15 million babies are born prematurely, representing a preterm birth rate of 11.1% [3]. Advances in neonatology over the last few decades have resulted in in-

Several predictive tests are currently being marketed for preterm birth. The clinical utility of these tests in prediction is often very confusing as studies are often conflicting and dependent on the population studied. This review explores both the current predictive tests used in clinical practice, as well as novel emerging tests, and discusses the clinical utility of these tests in relation to the different groups of women at risk of preterm delivery.

L'influenza del microbiota vaginale sulla nascita pretermine: una revisione sistematica e raccomandazioni per un set di dati minimo per la ricerca futura

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- CONCLUSIONS
- We have demonstrated that there is a paucity of molecular based, culture-independent studies that analyse the relationship between the vaginal microbiota and PTB as an outcome. The heterogeneity precluded a meta-analysis. Studies provide contradictory evidence and the quality of the clinical information in the studies is poor. To improve quality of future studies we have provided a database of essential and desirable items of quality that are method and topic specific.

Vi è scarsità di studi a base molecolare che collegano il microbiota vaginale al PTB.

Gli studi forniscono prove contraddittorie e la qualità delle informazioni cliniche è scarsa.

Studi più recenti mostrano un'associazione tra disbiosi vaginale e PTB.

Consigliamo un set di dati minimo per migliorare la qualità della ricerca futura.

Deve essere affrontato il ruolo di *L.iners* nell'eubiosi vaginale e nella disbiosi.

- Il pianeta TERRA si è formata circa 4 miliardi e 600 milioni di anni.
- I Batteri sono presenti sulla Terra da 3 miliardi e 600 milioni di anni.
- L’Homo Sapiens compare, dagli ultimi reperti paletnologici ritrovati in Marocco, circa 300.000 mila anni fa.
- *(E comincia già ad avere qualche problema!!!)*

“It is not the strongest of species that survive
Or the most intelligent, but the one most
Responsive to change.”

Darwin (1859)


GRAZIE