

Ecosistema e salute vaginale: prima difesa

Secondo Guaschino

Fiascherino, 11 maggio 2018

GENITOURINARY MUCOSAL DEFENSES



Vulvovaginal surface
Normal vaginal flora



Innate immunity



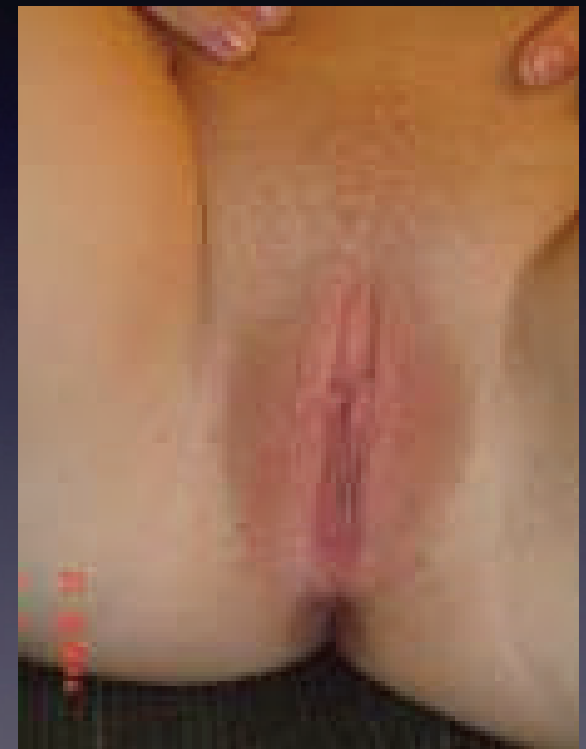
Acquired – adaptive immunity

Vulvar skin

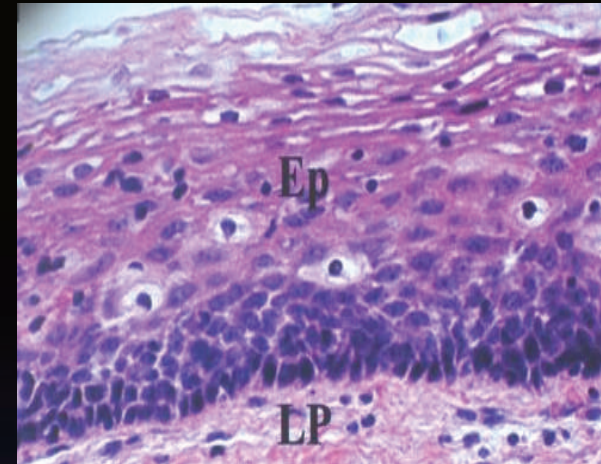
Prepubertal vulvar skin is fragile and at increased risk for mechanical injury as well as irritant and allergic reaction

Vulvar skin barrier function during the **reproductive years** is compromised by the environment

A decline in barrier function and immune decline are the essence of **postmenopausal** vulvar skin change



- 1- CORNIFIED LAYER
- 2- TRANSITIONAL LAYER
- 3- COLUMNAR o GLANDULAR



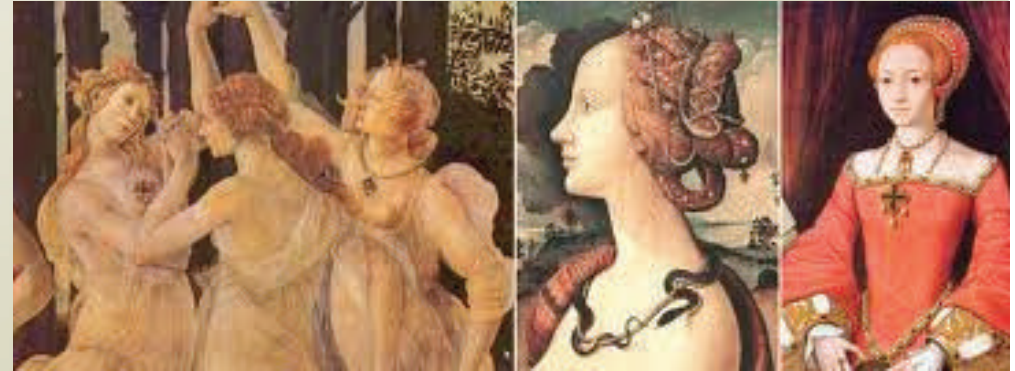
- Corneification
- Exterior lipid enveloped
 - Cadherins
- Intracellular desmosomes
 - GAP junctions

CORNIFIED
LAYER

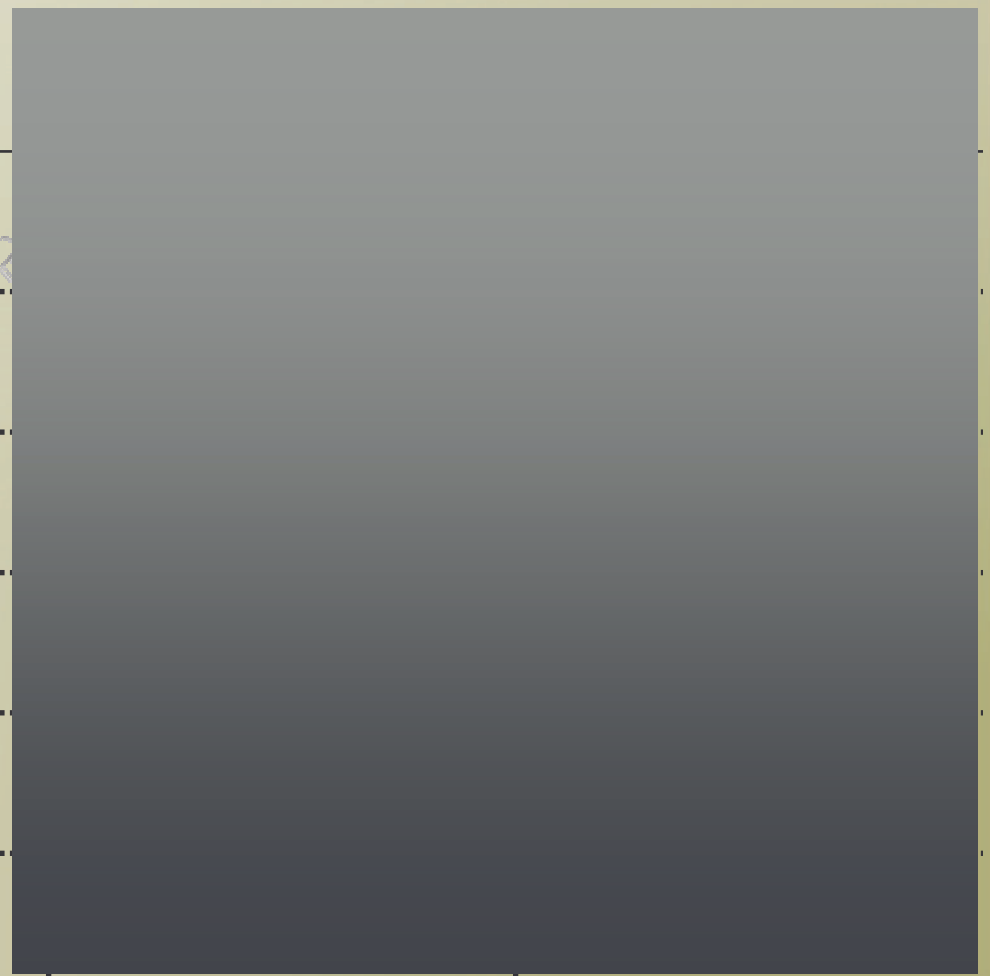
- Simple Layer
- Mucin-secreting
glands

SIMPLE
COLUMNAR
EPITHELIUM

VAGINAL MILIEU

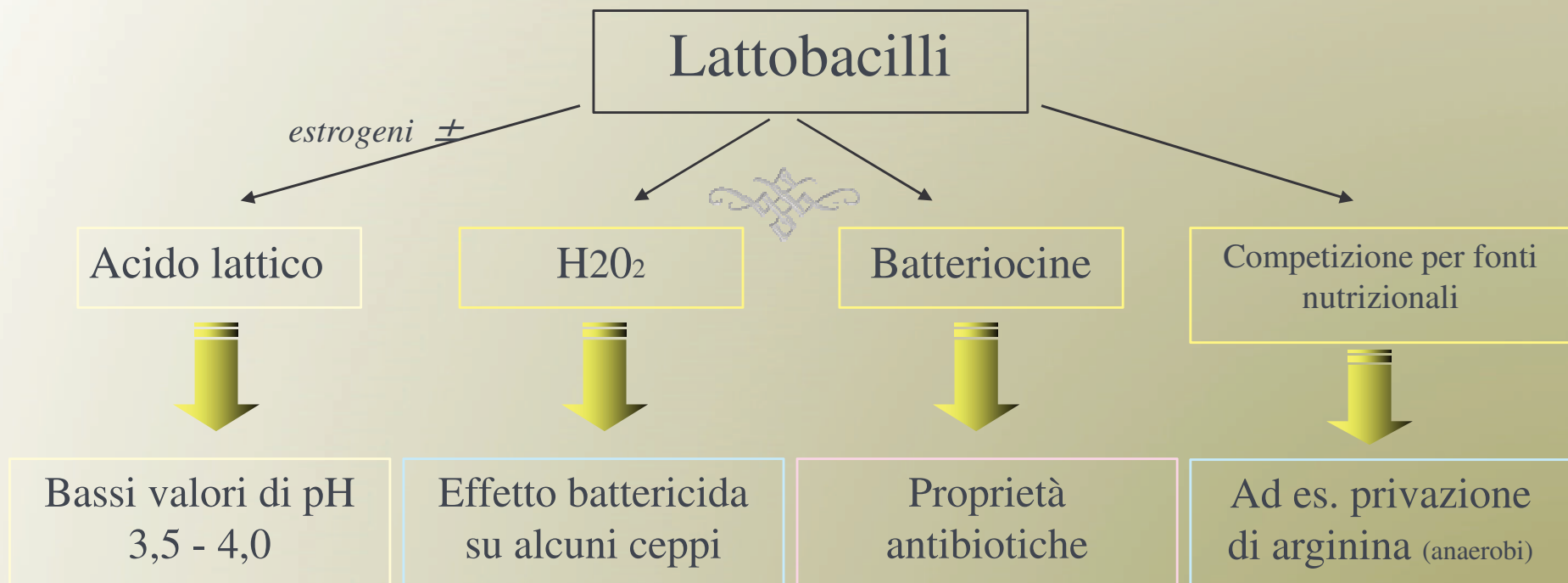


	Normal
H2O2 Lattobacilli	Predominant
Total microorganisms	7 10
Anaerob/aerob	2 to 5: 1
Gardnerella	5 - 60%
Micoplasma	15 - 30 %
Others	5 - 20 %



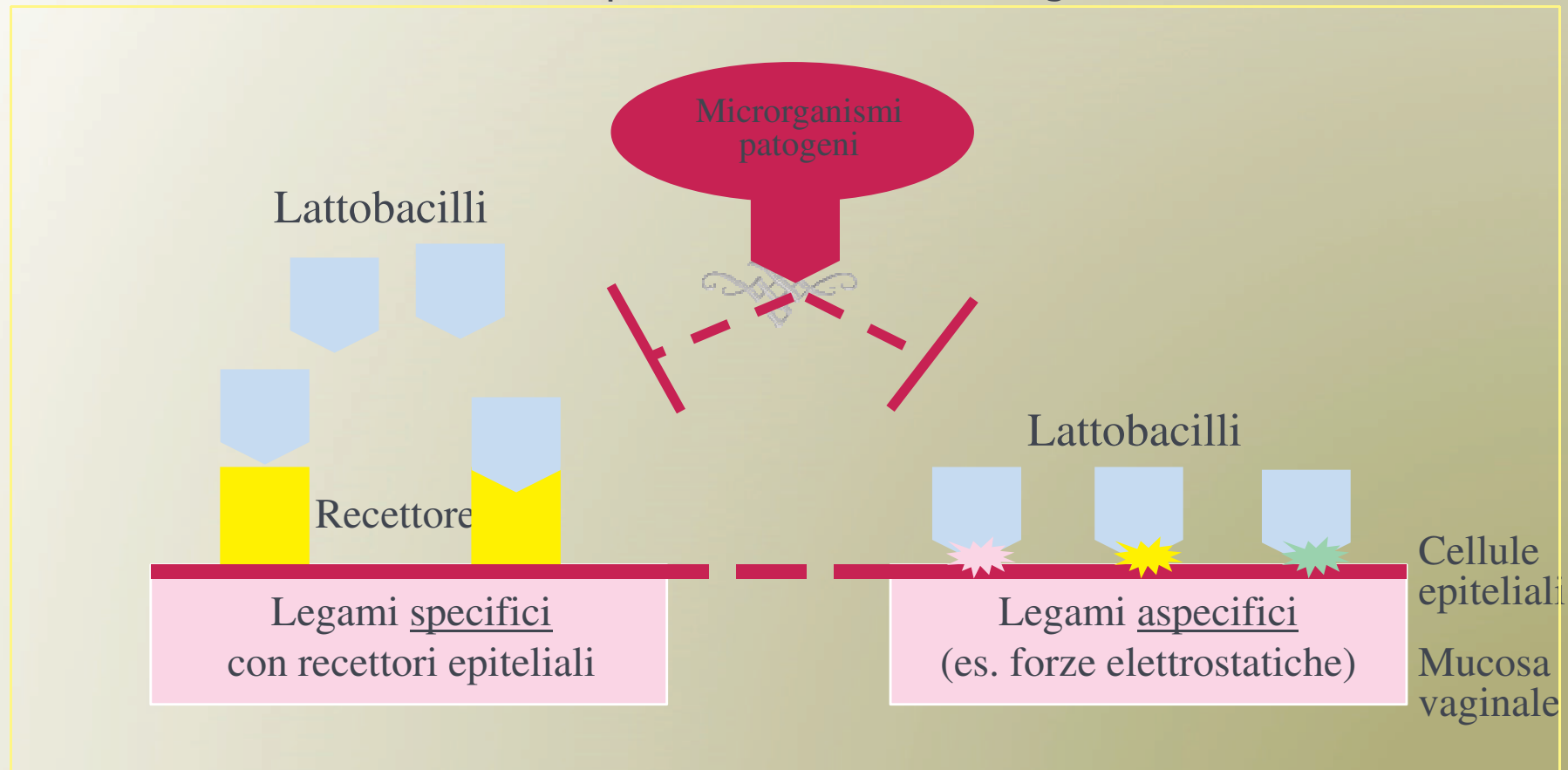
Inibizione della crescita dei patogeni

I lattobacilli sintetizzano sostanze fondamentali per il mantenimento di un corretto equilibrio nell'ecosistema vaginale...



Inibizione dell'adesione dei patogeni alla mucosa vaginale

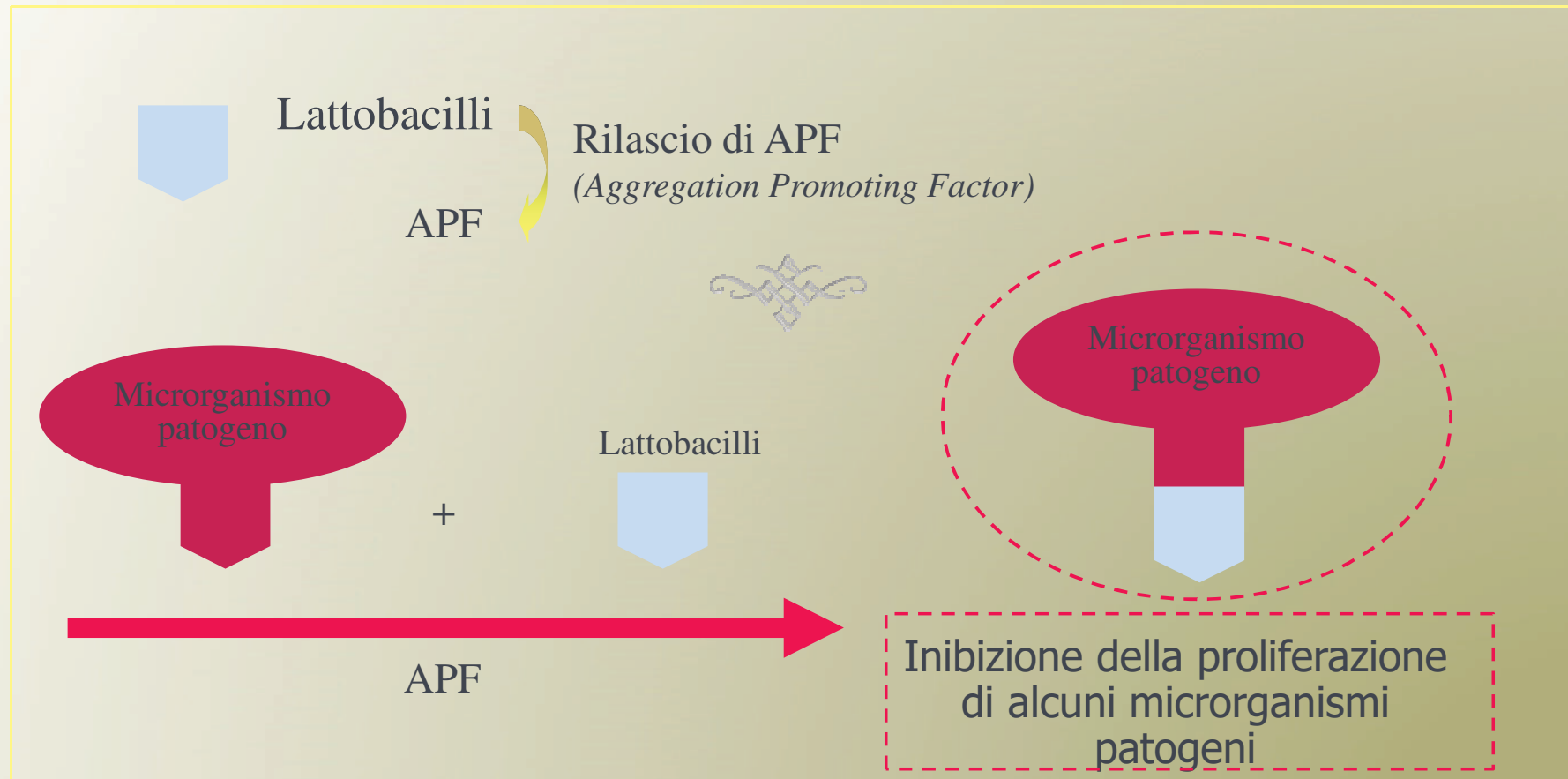
I lattobacilli si legano in modo specifico e aspecifico alle cellule epiteliali della mucosa vaginale...



... ed impediscono ai microrganismi patogeni di trovare liberi i siti di legame e quindi aderire alla mucosa vaginale

Inibizione della moltiplicazione dei patogeni

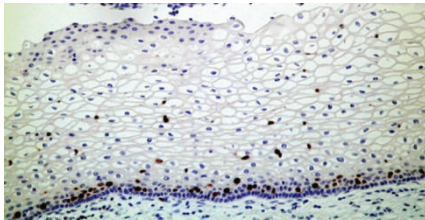
I lattobacilli interagiscono con diversi ceppi di microrganismi patogeni (es. *C. albicans*, *E. coli*)...



... e rilasciano un fattore (APF)
che favorisce la co-aggregazione tra lattobacilli e patogeni

Lactobacilli : Historical view

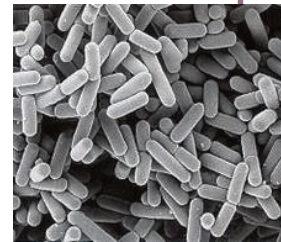
Estrogen



Glycogen



Lactobacilli



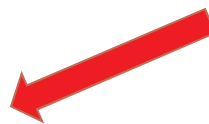
Production of antimicrobial substances

- H_2O_2
- Bacteriocins
- Biosurfactant

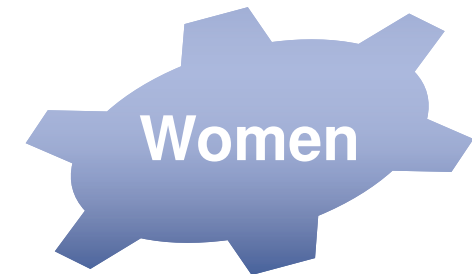
Lactic acid



pH 3.8-4.5



Inhibits growth of pathogenic bacteria








Estrogen

Epithelium

Glicogen

pH

Microbiota

Premenarche	+		+	6	Aerobes Anaerobes
Fertile age	++++		++	3,5 - 4	Lattobacilli Gardnerella
Pregnancy	++++		++	3,5 - 4	Lattobacilli Gardnerella, GBS
Menopause	+		-	6	Aerobes E Coli Anaerobes
Menopause ET	+		-	3,5 - 4	Lattobacilli Gardnerella

FDS

NEW FINDINGS ABOUT VAGINAL BACTERIAL FLORA

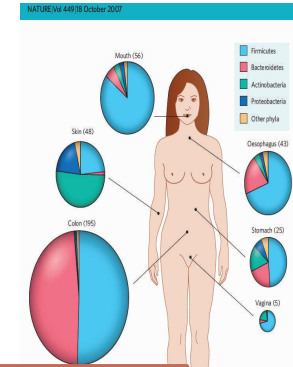
IARA MORENO LINHARES^{1*}, PAULO CESAR GIRALDO², EDMUND CHADA BARACAT³

Study conducted at Disciplina de Ginecologia da Faculdade de Medicina da Universidade de São Paulo – FMUSP, São Paulo, SP, Brazil

nized the study of microorganisms. The use of amplification, cloning techniques and subsequent analysis of sequences of bacterial genes (genes that codify for bacterial rRNA 16 S) in samples of vaginal fluid have allowed the identification of the majority of common species of *Lactobacilli* and other microorganisms. Thus, these techniques have demonstrated that *Lactobacilli sp* do not always correspond to the dominant species in the vagina of healthy women. Besides that, vaginal environment inhabitants until then unknown have been identified.^{2,4}

Indigenous Microbiota

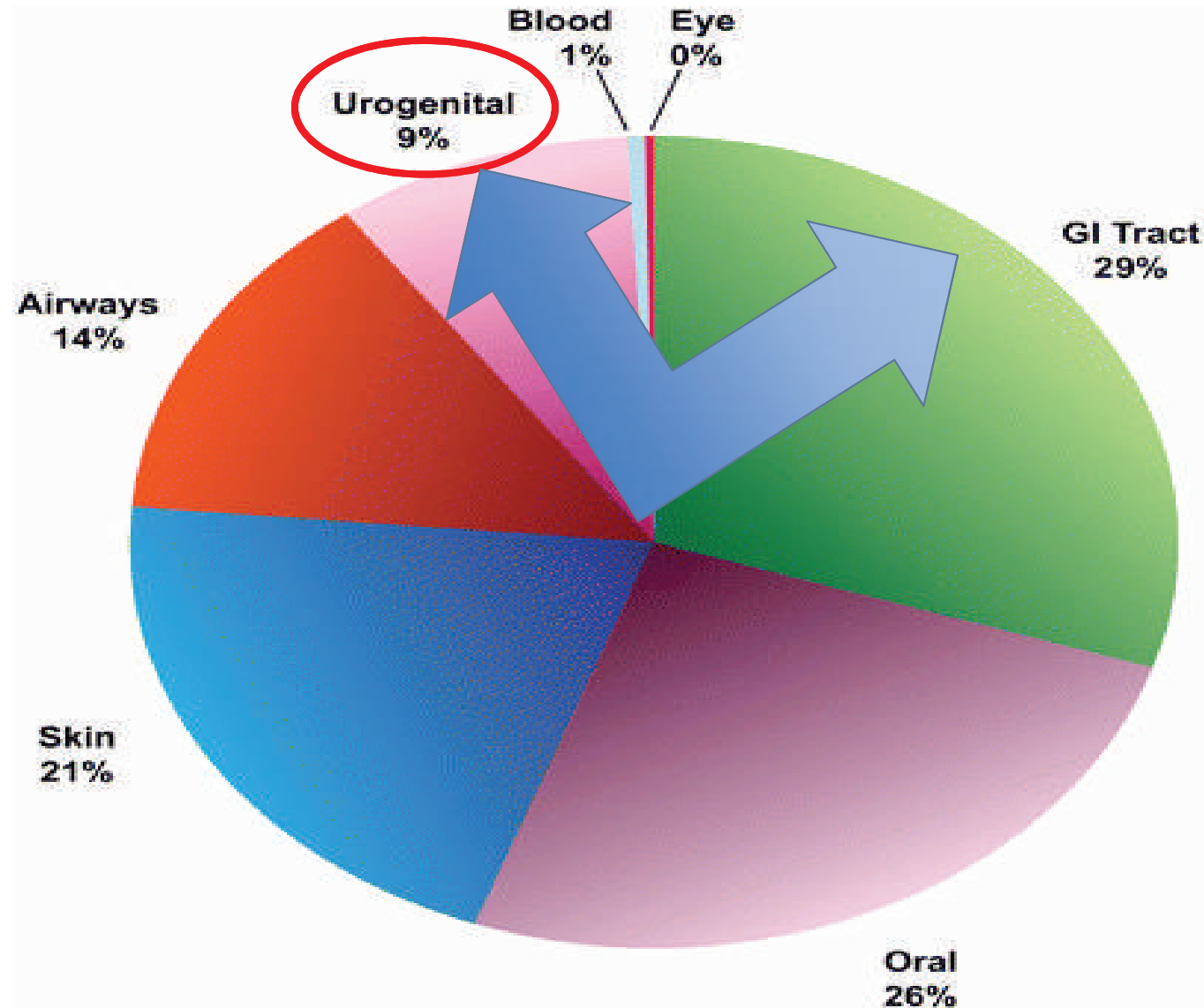
The Human Microbiome Project
Nature, 2007



- 3% individual's total body mass
- 10 times more numerous than our own cells
- 100 times more genes
- Culture-based methods allow to recover <30% of total microorganisms

**“Microbiota
(and also vaginal
microbiota)
is the ecological
community of
commensal, symbiotic,
and pathogenic
microorganisms that
literally share our body
space”.**

Bacteria distribution in the human body



Indigenous Vaginal Microbiota

Review Article

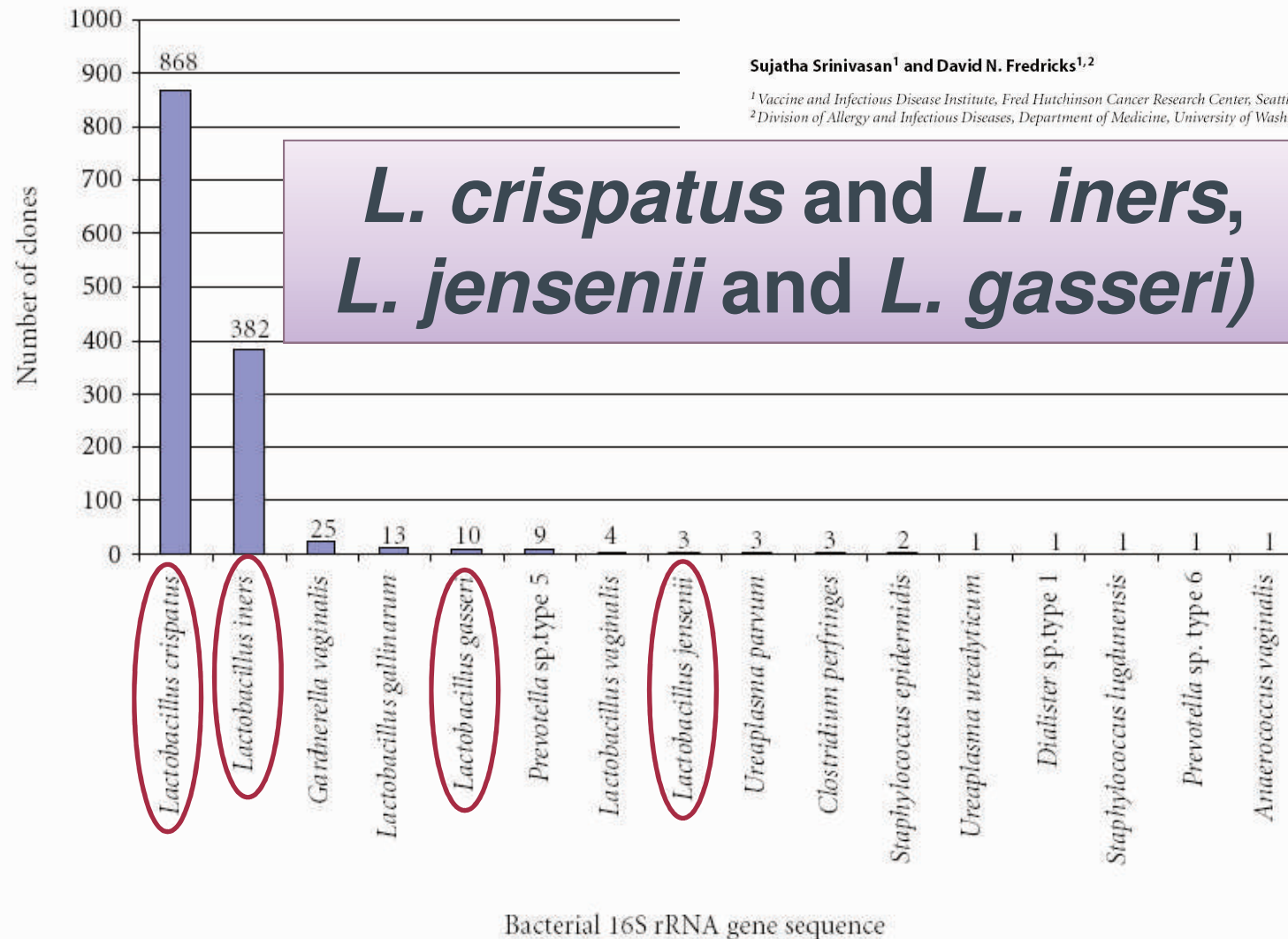
Hindawi Publishing Corporation
Interdisciplinary Perspectives on Infectious Diseases
Volume 2008, Article ID 750479, 22 pages

The Human Vaginal Bacterial Biota and Bacterial Vaginosis

Sujatha Srinivasan¹ and David N. Fredricks^{1,2}

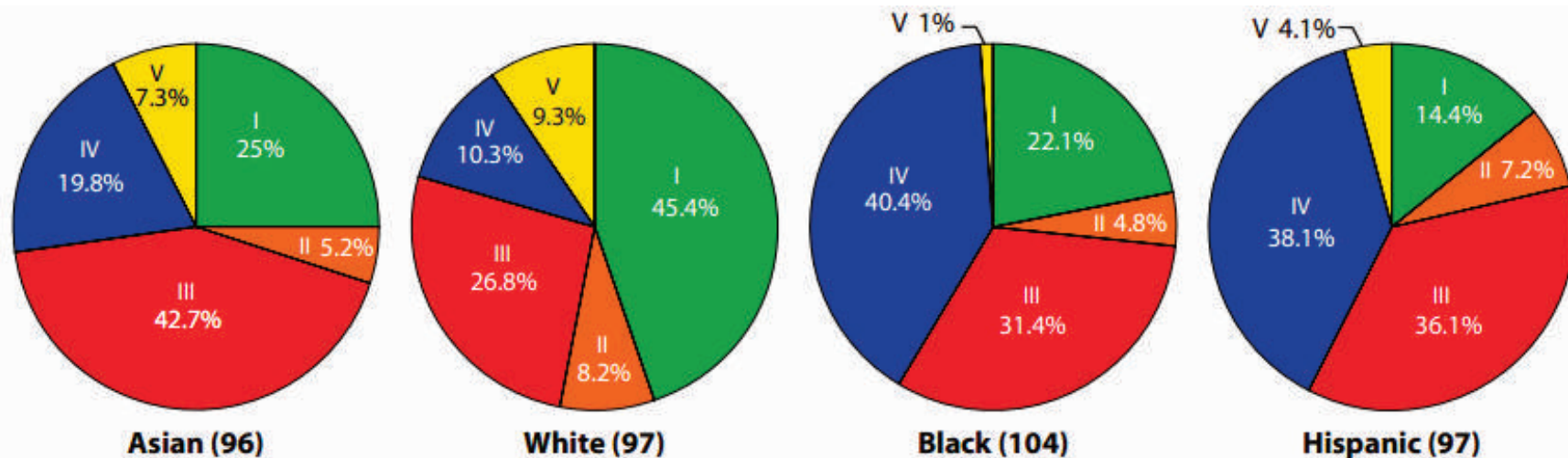
¹ Vaccine and Infectious Disease Institute, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA

² Division of Allergy and Infectious Diseases, Department of Medicine, University of Washington, Seattle, WA 98195, USA



Vaginal microbiome of reproductive-age women

Jacques Ravel^{a,1}, Pawel Gajer^a, Zaid Abdo^b, G. Maria Schneider^c, Sara S. K. Koenig^a, Stacey L. McCulle^a, Shara Karlebach^d, Reshma Gorle^e, Jennifer Russell^f, Carol O. Tacket^f, Rebecca M. Brotman^a, Catherine C. Davis^g, Kevin Ault^d, Ligia Peralta^e, and Larry J. Forney^{c,1}



Community groups I, II, III, and V are predominated by *Lactobacillus crispatus*, *L. gasseri*, *L. iners*, and *L. jensenii*, respectively, while community group IV contains a diverse assemblage of facultative and strictly anaerobic bacteria

DIFFERENT COMPOSITION IN DIFFERENT ETHNICITIES

pH of vaginal community groups in women of different ethnicities

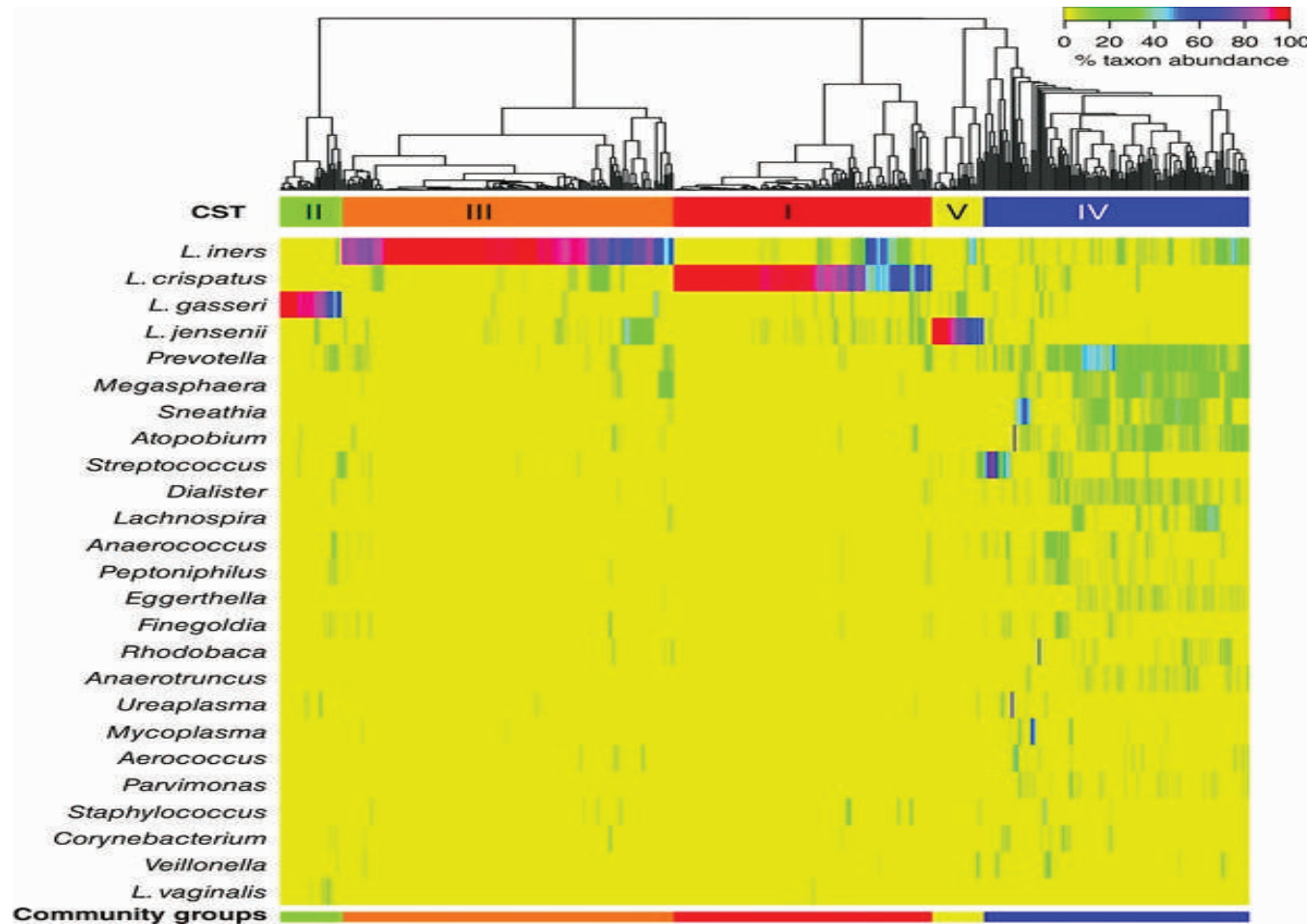
Ethnic groups	Community groups											
	I (<i>L. crispatus</i>)		II (<i>L. gasseri</i>)		III (<i>L. iners</i>)		IV (Diversity group)		V (<i>L. jensenii</i>)		All groups	
	Subjects [†]	pH [‡]	Subjects [†]	pH [‡]	Subjects [†]	pH [‡]	Subjects [†]	pH [‡]	Subjects [†]	pH [‡]	Subjects [†]	pH [‡]
Asian	24	4.4 ± 0.52	5	4.4 ± 0.44	41	4.0 ± 0.0	19	5.5 ± 0.44	7	5.0 ± 0.8	96	4.4 ± 0.59
White	44	4.0 ± 0.0	8	4.7 ± 0.44	26	4.3 ± 0.30	10	5.5 ± 0.74	9	4.85 ± 0.22	97	4.2 ± 0.30
Black	23	4.0 ± 0.0	5	5.0 ± 0.0	33	4.0 ± 0.0	42	5.3 ± 0.44	1	4.7 ± 0.4	104	4.7 ± 1.04
Hispanic	14	4.0 ± 0.0	7	4.7 ± 0.22	35	4.4 ± 0.59	37	5.3 ± 0.44	4	5.0 ± 0.5	97	5.0 ± 0.74
All ethnic groups	105	4.0 ± 0.3	25	5.0 ± 0.7	135	4.4 ± 0.6	108	5.3 ± 0.6	21	4.7 ± 0.4	394	4.4 ± 0.7

Vaginal microbiome of reproductive-age women
Ravel et al. PNAS | March 15, 2011 | vol. 108 | suppl.

1

versa. Profiles of vaginal microbiota have been reported to be associated with race/ethnicity [15, 18], level of education [34], use of hormonal contraceptives [35, 36], use of feminine hygiene products [37], gender of sexual partners [35, 38], number of sexual partners [39], condom use [35, 39], sexual behaviours [39] and smoking [38]. Some factors, such as level of edu-

Heat map of vaginal microbiota community state types



Steven B Smith and Jacques Ravel, 2017

Microbial stimulation of PRRs initiates cytokine/chemokine signalling cascades, for example secretion of interleukin (IL)-1 β , IL-6, IL-8 and tumor necrosis factor- α (TNF- α), in order to recruit or activate specialized cells, such as NK cells, macrophages, CD4+ helper T-cells, and CD8+ cytotoxic T-cell lymphocytes and B lymphocytes

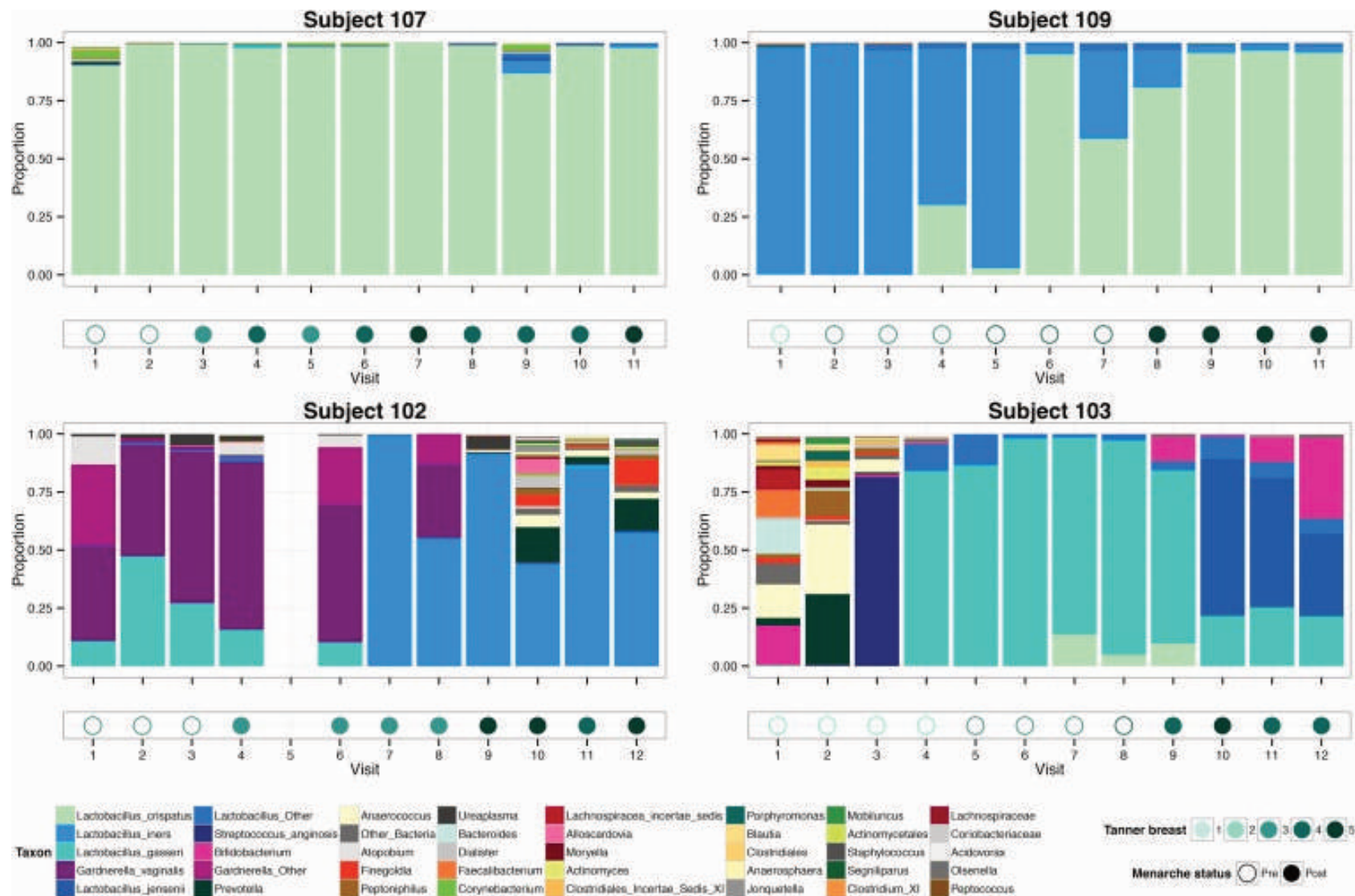
These studies continue to support the notion that the innate immune response is largely driven by vaginal bacterial community states, with CST-IV potentially having a larger pro-inflammatory response than CST-I or CST-II, and with CST-III triggering an intermediate response.

Thus, a change in vaginal community composition and function is strongly associated with the integrity of the protective mucus layer. Therefore, vaginal bacteria can reduce or increase susceptibility to infectious agents such as HIV

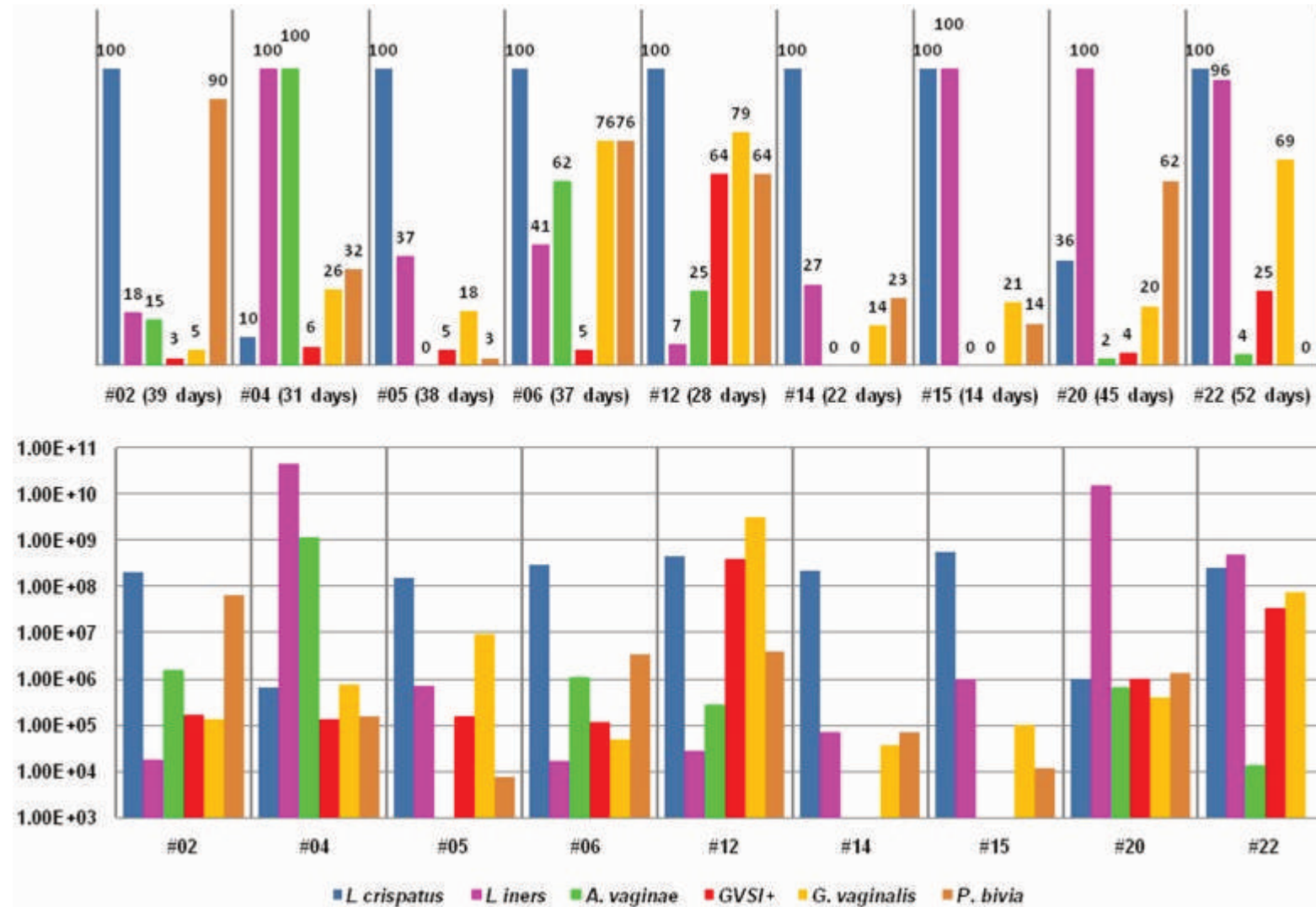
The vaginal ecosystem is highly dynamic and individualized with both temporal and interindividual differences

Establishment of *Lactobacillus* dominance does not necessarily result in static community composition.

Multiple species of *Lactobacillus* may be numerically dominant at different times in the same individual, consistent with observations in adult women.

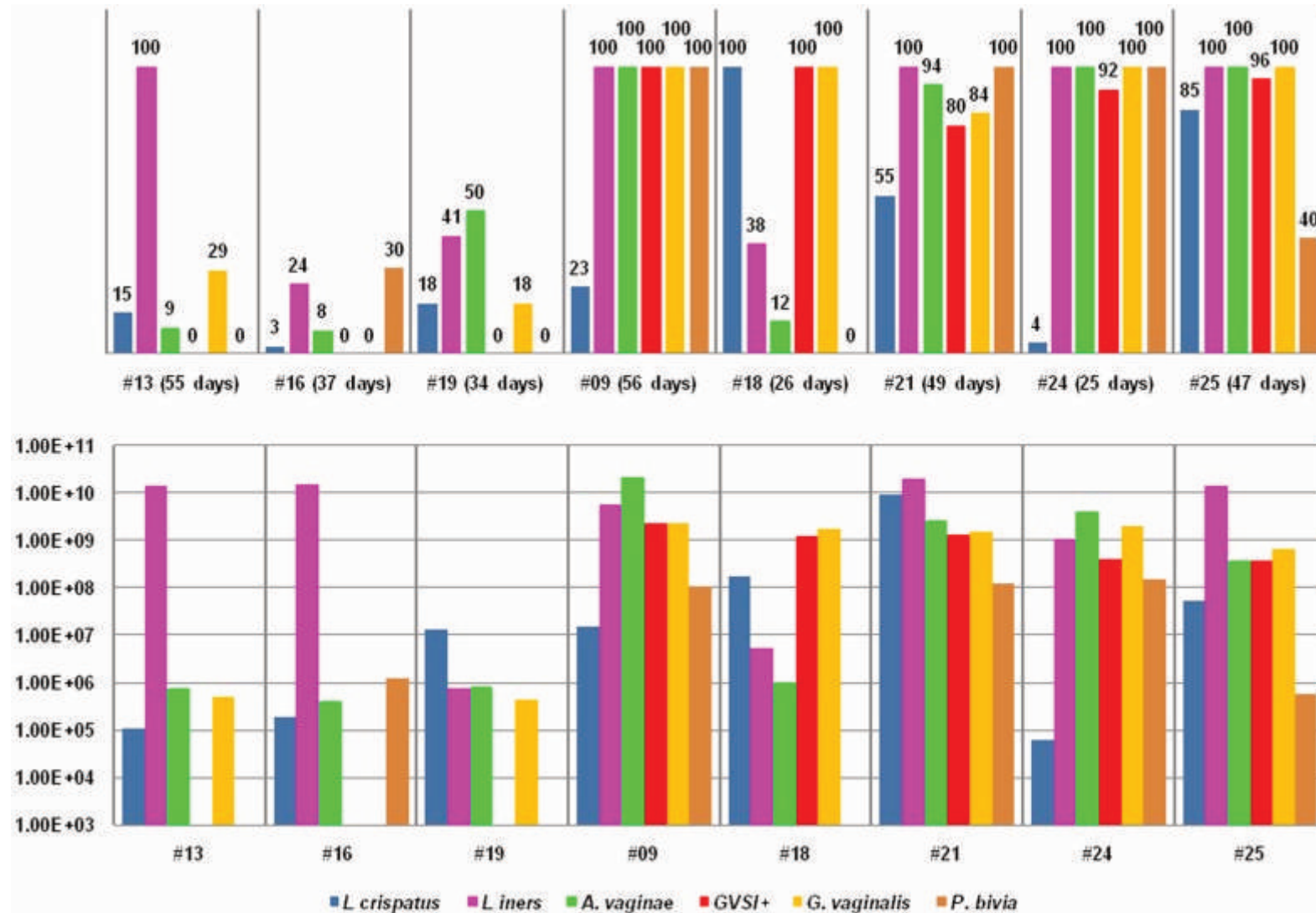


Roxana J. Hickey et al, 2015



The presence and average concentrations of the 5 species during the study in group N.

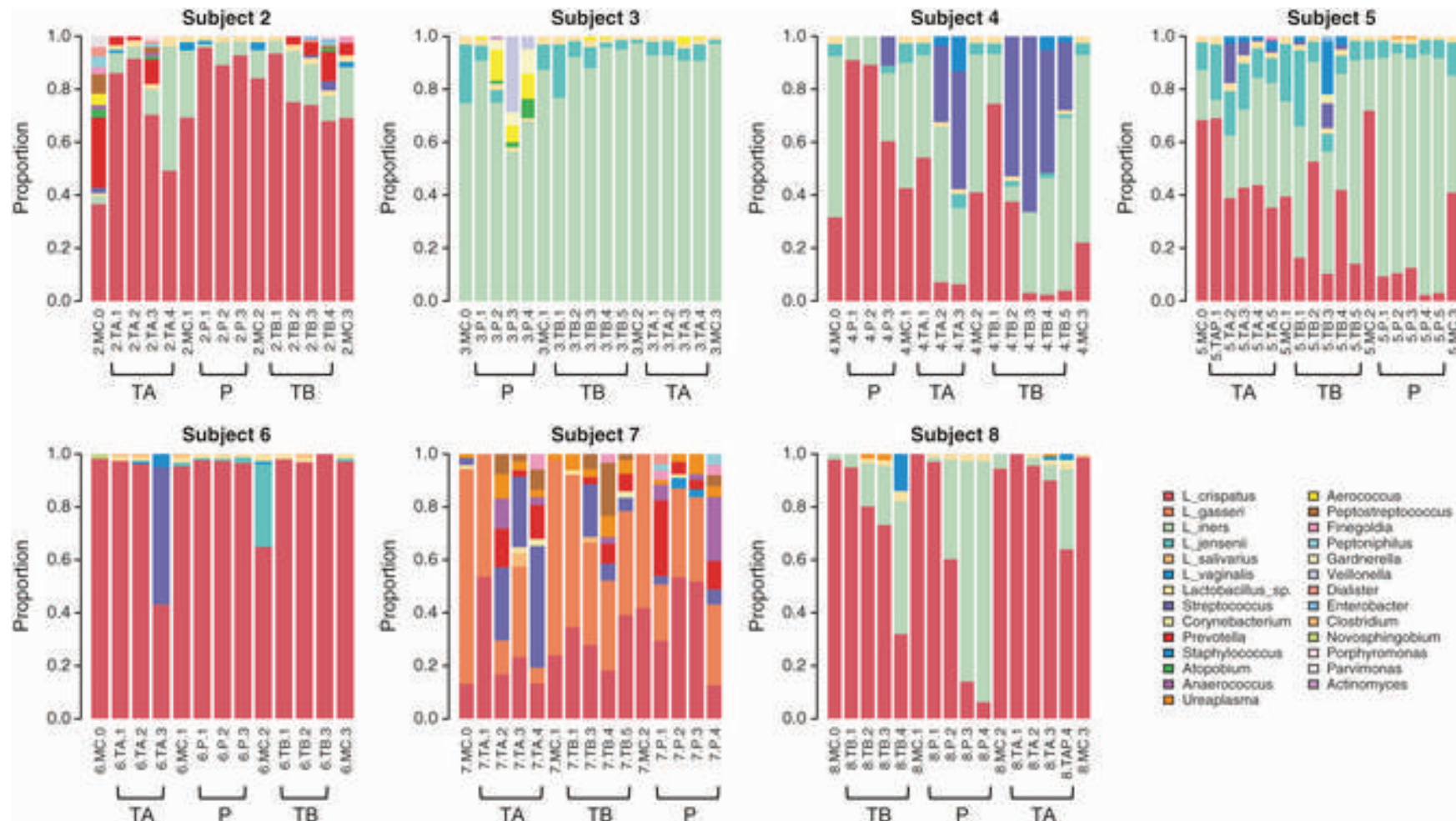
Guido Lopes dos Santos Santiago et al., 2012



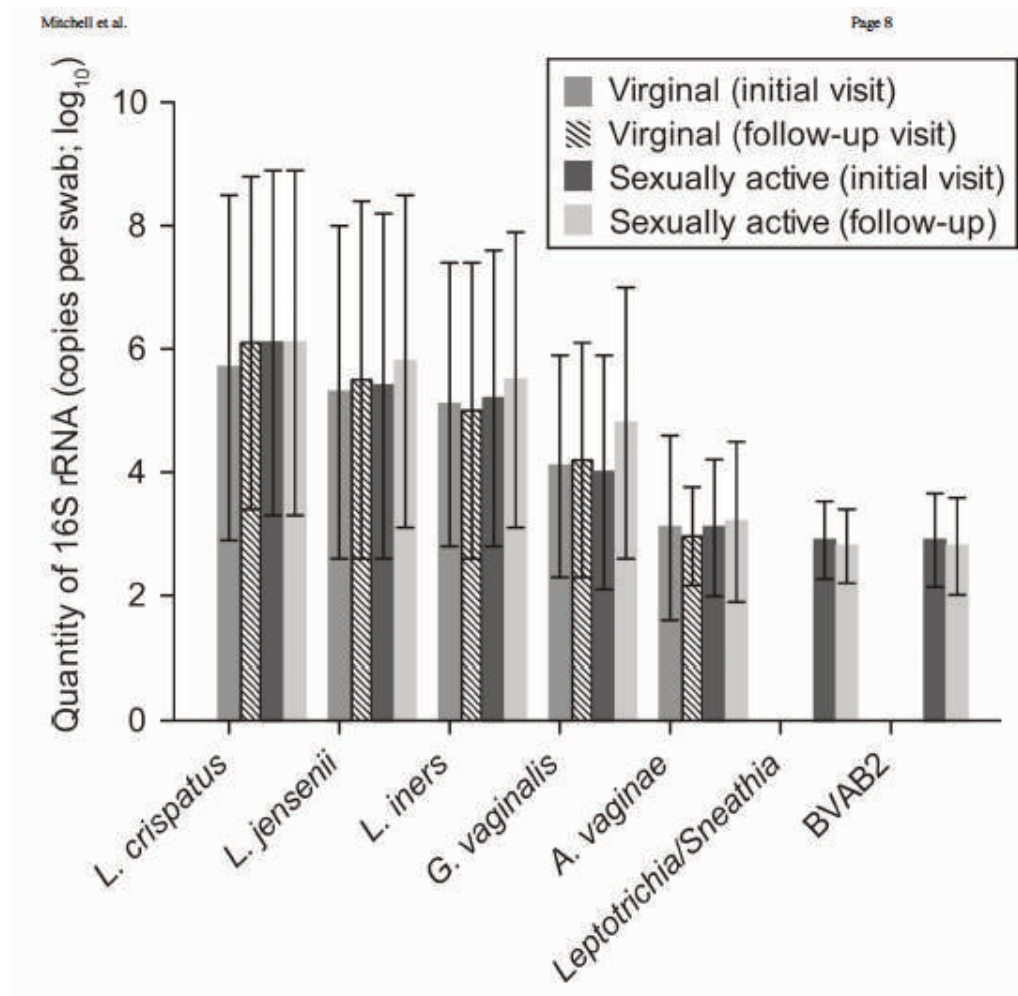
The presence and average concentrations of the 5 species during the study in group D.

Guido Lopes dos Santos Santiago et al., 2012

Effects of tampons and menses on the composition and diversity of vaginal microbial communities over time



Sexual activity, as well as menses, may play a role in disrupting or changing the vaginal microbial environment



Obstet Gynecol. 2012 December ; 120(6): 1306–1313.

Effect of Sexual Debut on Vaginal Microbiota in a Cohort of Young Women

Caroline M. Mitchell, MD MPH¹, David N. Fredricks, MD², Rachel L. Winer, PhD³, and Laura Koutsky, PhD³



Effect of Sexual Debut on Vaginal Microbiota in a Cohort of Young Women

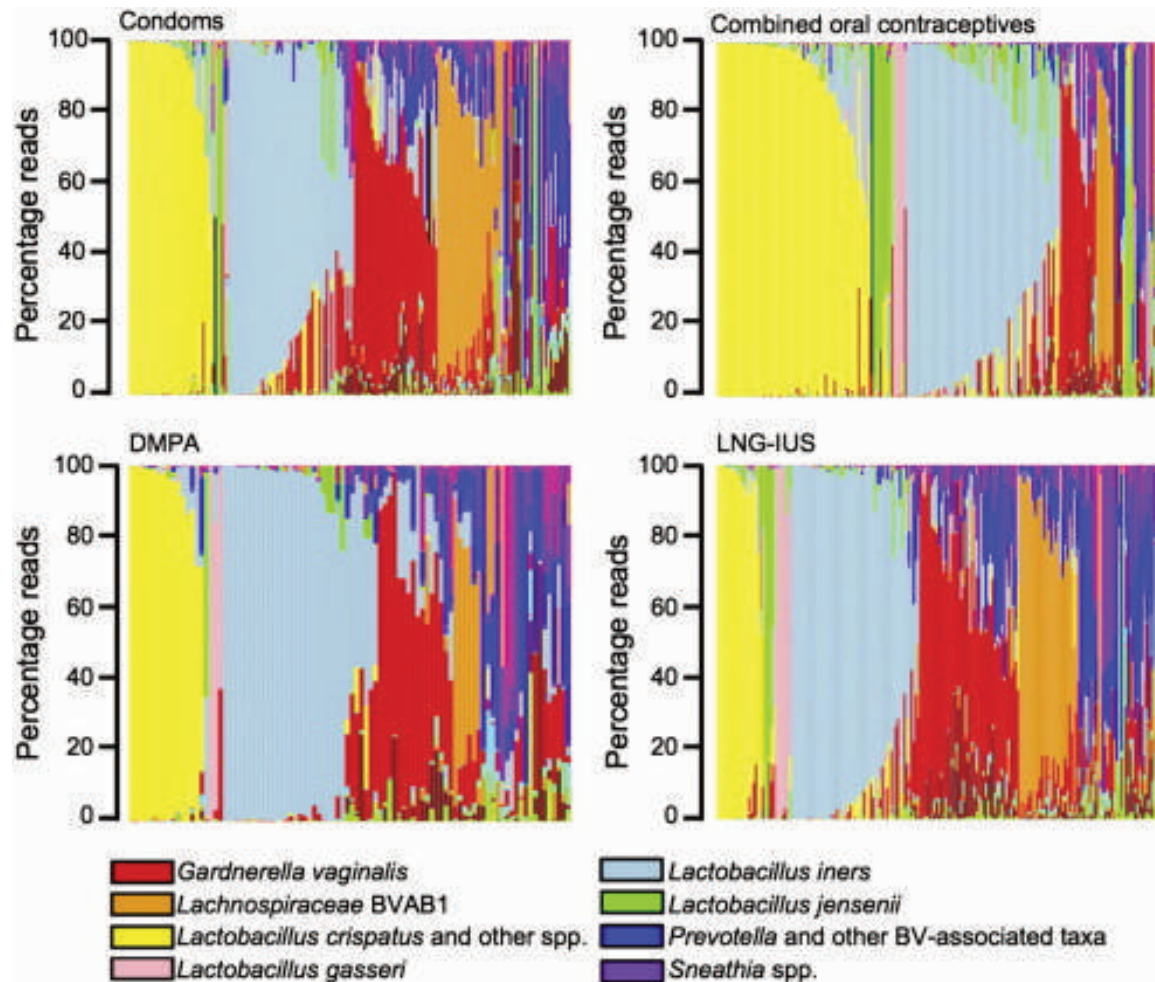
Caroline M. Mitchell, MD MPH¹, David N. Fredricks, MD², Rachel L. Winer, PhD³, and Laura Koutsky, PhD³

Interestingly, in our data, women who remained virginal had very stable microbiota, while those who became sexually active began to show some variability in bacterial composition though not to the extent reported in older women. This suggests that sexual activity, as well as menses, may play a role in disrupting or changing the vaginal microbial environment, though via what mechanism is not clear.

Obstet Gynecol. 2012 December ; 120(6): 1306–1313.

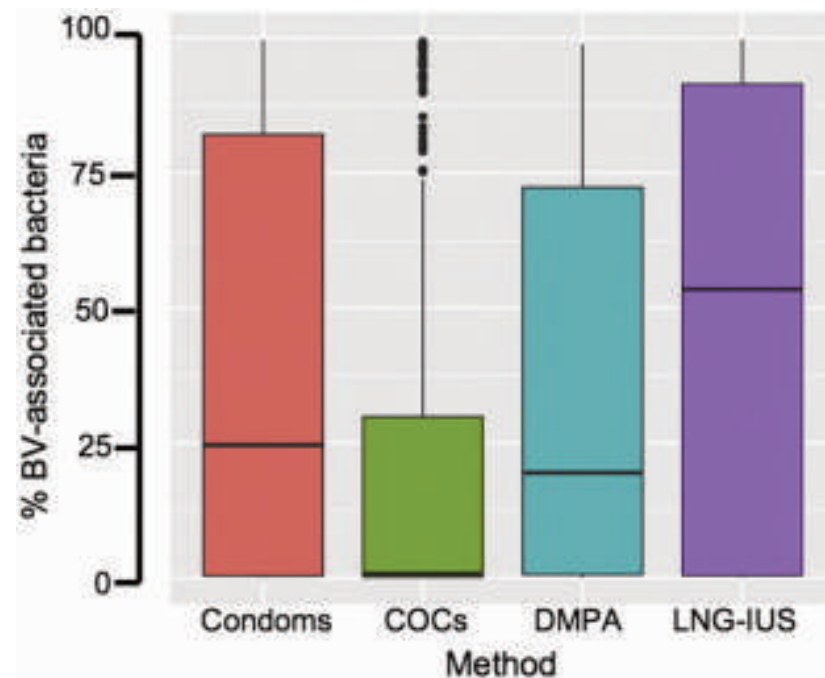
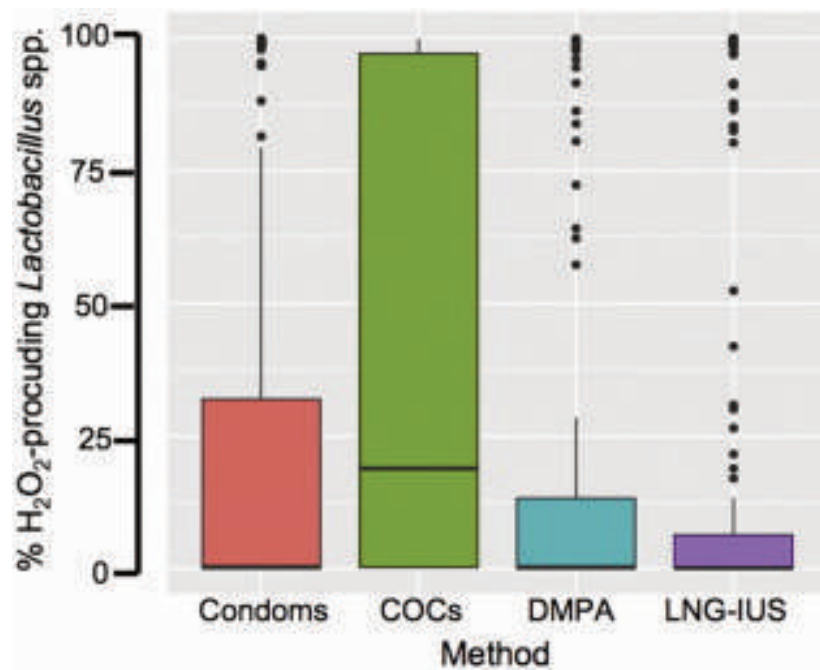
Effects of combined oral contraceptives, depot medroxyprogesterone acetate and the levonorgestrel-releasing intrauterine system on the vaginal microbiome

J. Paul Brooks et al.



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Microbiota and Menopause in urogenital tract

- Increase of Anaerobes !
- Increase of E Coli
- Lactobacilli deficiency !
- Immunological imbalance !
- Tissue alterations !



ALTERATION OF UROGENITAL MICROBIOTA

The Vaginal Microbiota: What Have We Learned after a Decade of Molecular Characterization?

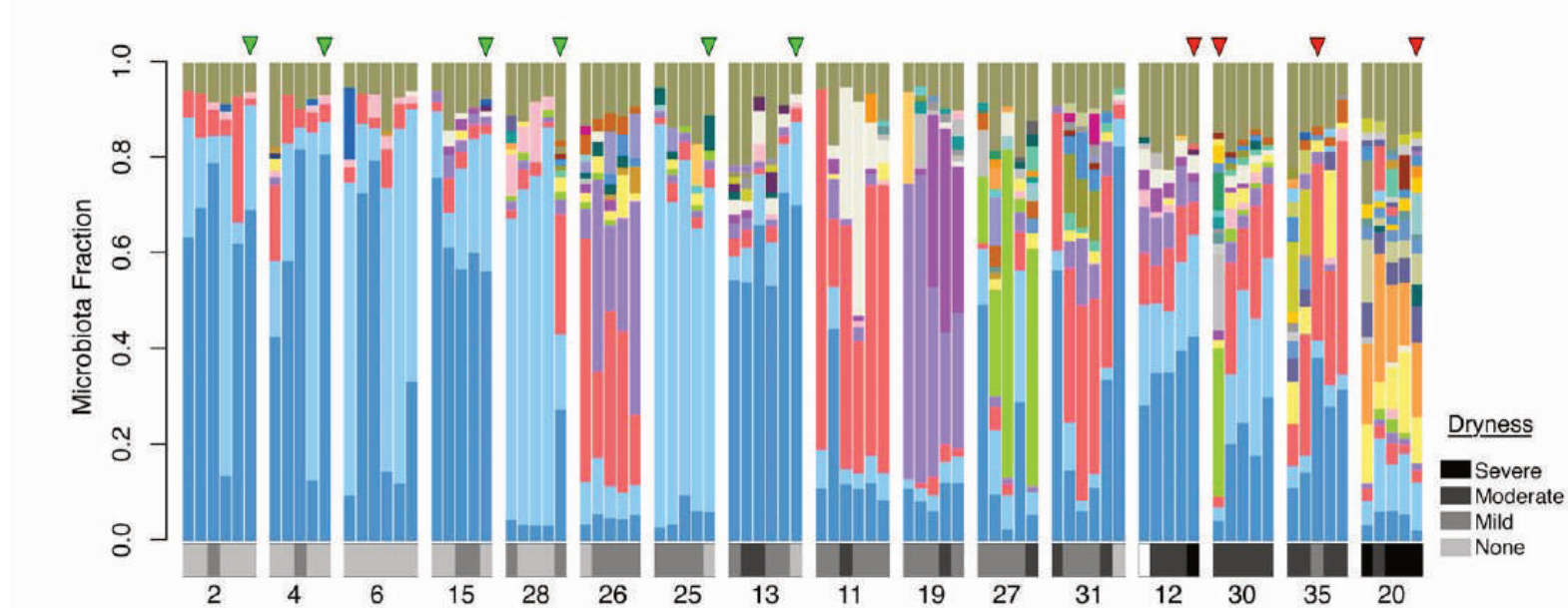
Janneke H. H. M. van de Wijgert^{1*}, Hanneke Borgdorff², Rita Verhelst³, Tania Crucitti⁴, Suzanna Francis⁵, Hans Verstraelen⁶, Vicky Jespers⁴

It is worth emphasizing that the molecular studies did not identify large VMB differences between adolescent, reproductive age, and post-menopausal women [24,79], except in post-menopausal women with vaginal atrophy and dryness [49]. Post-menopausal women have lower estrogen levels, which might lead to less protection from dysbiosis. However, they no longer menstruate, and are therefore protected from the potentially negative effects of menstrual blood and increased vaginal pH on the VMB.

The Vaginal Microbiota:

Vaginal Microbiome and Epithelial Gene Array in Post-Menopausal Women with Moderate to Severe Dryness

Ruben Hummelen^{1,2§}, Jean M. Macklaim^{1,3§}, Jordan E. Bisanz^{1,4§}, Jo-Anne Hammond^{1,5}, Amy McMillan^{1,4}, Rebecca Vongsa⁶, David Koenig⁶, Gregory B. Gloor^{1,3¶}, Gregor Reid^{1,4*}



reported previously. There was an inverse correlation between *Lactobacillus* ratio and dryness, a condition commonly found after menopause, which shown here to be associated with changes in vaginal epithelial cell integrity and inflammation.

CONCLUSIONS

- The human vaginal ecosystem is a dynamic environment in which microbes can affect host physiology but also where host physiology can affect the composition and function of the vaginal microbiota.
- The inconsistent innate immune response is observed with non-Lactobacillus- or *L. iners*-dominated microbiota (CST-IV, BV, AV and CST-III, respectively). Thus, a change in vaginal community composition and function is strongly associated with the integrity of the protective mucus layer.
- Although engagement in penile-vaginal sex did not appear to result in a persistent change in the consistency of vaginal microbial communities over time, it was associated with increased *G. vaginalis* clade diversity in young women with and without BV, supporting sexual transmission of commensal and potentially pathogenic clades of *G. vaginalis*.
- COC use may positively influence gynecologic health through an increase in healthy lactobacilli and a decrease in BV associated bacterial taxa.

DYSBIOSIS IMPACT ON VAGINAL HEALTH.



Grazie per l'attenzione !!!

