Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore

Gemelli

Microbioma e ambiente vaginale una stretta relazione; cosa cambia prima e dopo la menopausa

Inbal D. Amar MD. PhD

La menopausa da un'altra prospettiva

Foto: Arte de Nina Millen

Sabato 7 dicembre 2019

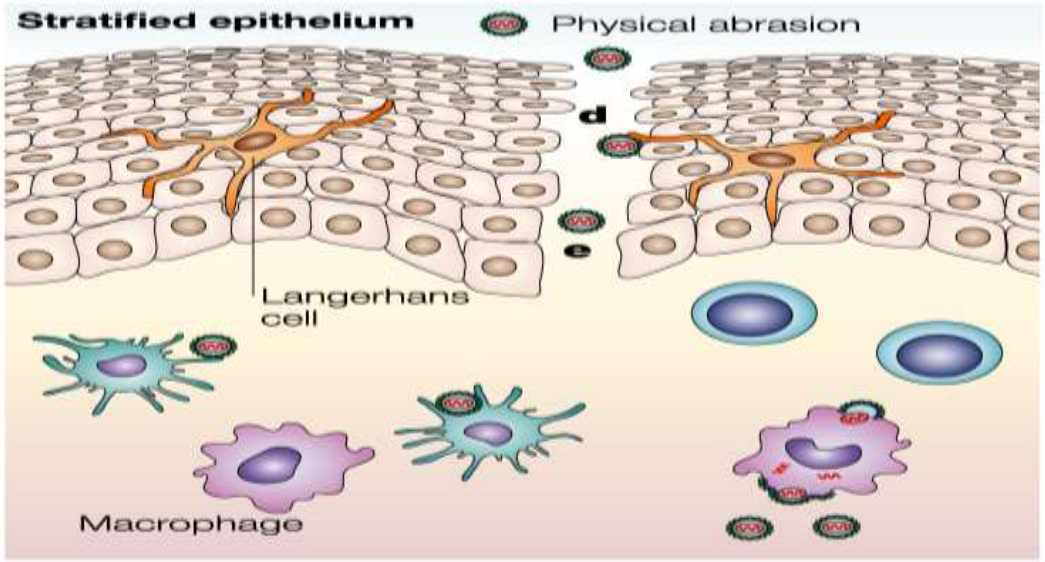
Bonus Pastor

via Aurelia, 208, Roma

Microbiota Vaginale

Il Microbiota vaginale è dominato dalla presenza di differenti specie di lattobacilli che insieme costituiscono "la **flora di Doderleïn**"

- Lactobacillus *rhamnosus*
- Lactobacillus *acidophilus*
- Lactobacillus *fermentum*
- Lactobacillus *reuteri*
- Lactobacillus *plantarum*
- Lactobacillus *brevis*
- Lactobacillus *salivarius*
- Lactobacillus *casei*
- Lactobacillus *cellobiosus*
- Lactobacillus *crispatus*
- Lactobacillus *jensenii*
- Lactobacillus *iners*
- Lactobacillus *gasseri*



10^9 UFC/ml di batteri prevalentemente Lattobacilli

J. P. Lepargneur et al. - *J. Gynecol. Biol. Reprod., 31: 485-494,2002*

Microbiota Vaginale

….non solo Lattobacilli

AEROBI

- Corynebacterium
- Streptococcus
- Gadnerella *vaginalis*
- Enterococcus
- Enterobacteriaceae
- Mycoplasma *hominis*
- Yeast
- Candida
- Staphylococcus *aureus*
- Escherichia *coli*
- Klebsiella *pneumonie*
- Staphylococcus *epidermidis*

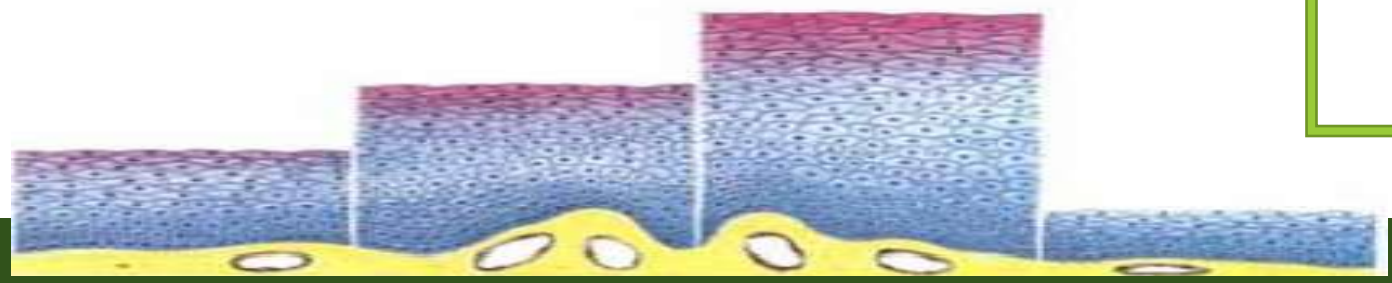
ANAEROBI

- Peptococcus
- Peptostreptococcus
- Eubacterium
- Bacteroides *spp*
- Fusobacterium
- Veillonella
- Bifidobacterium
- Clostridium
- Ureaplasma *spp*
- Mobiluncus
- Prevotella
- Micoplasmi

. P. Lepargneur et al. - *J. Gynecol. Biol. Reprod., 31: 485-494,2002*

Ecosistema Vaginale

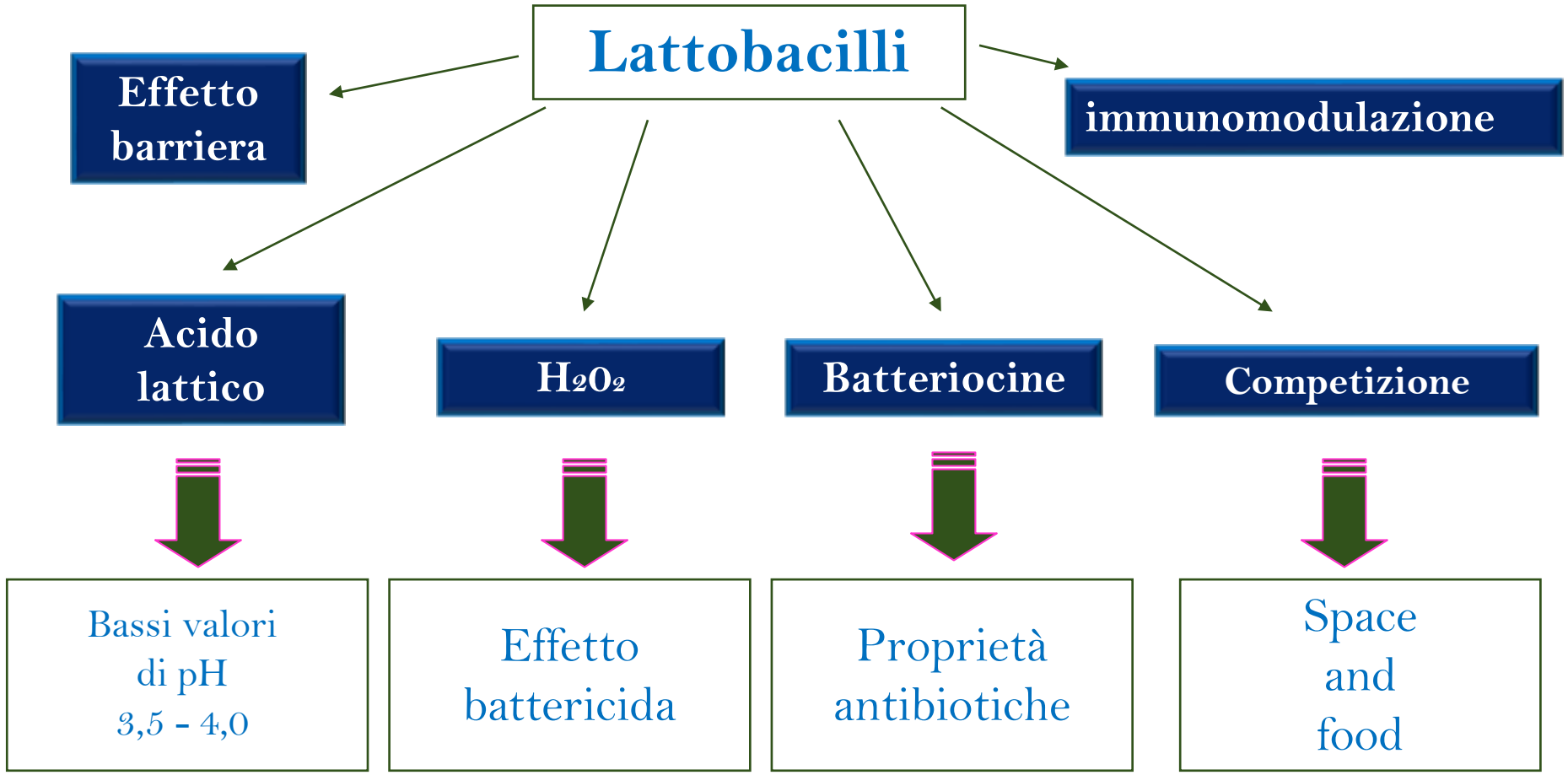
ETA'	ESTROGENI	EPITELIO	GLICOGENO	pH	MICROBIOTA
neonatale	♦♦♦	⬭	+	4-5	Lattobacilli
prepubere	♦	⬭	–	7	Coliformi
fertile	♦♦♦♦	⬭	++	3.5-4	Lattobacilli
menopausale	♦	⬭	–	7	Coliformi



prepubere **fertile** **gravidanza** **menopausa**

Vaginal microbiota: **VMB**

Microbiota Vaginale



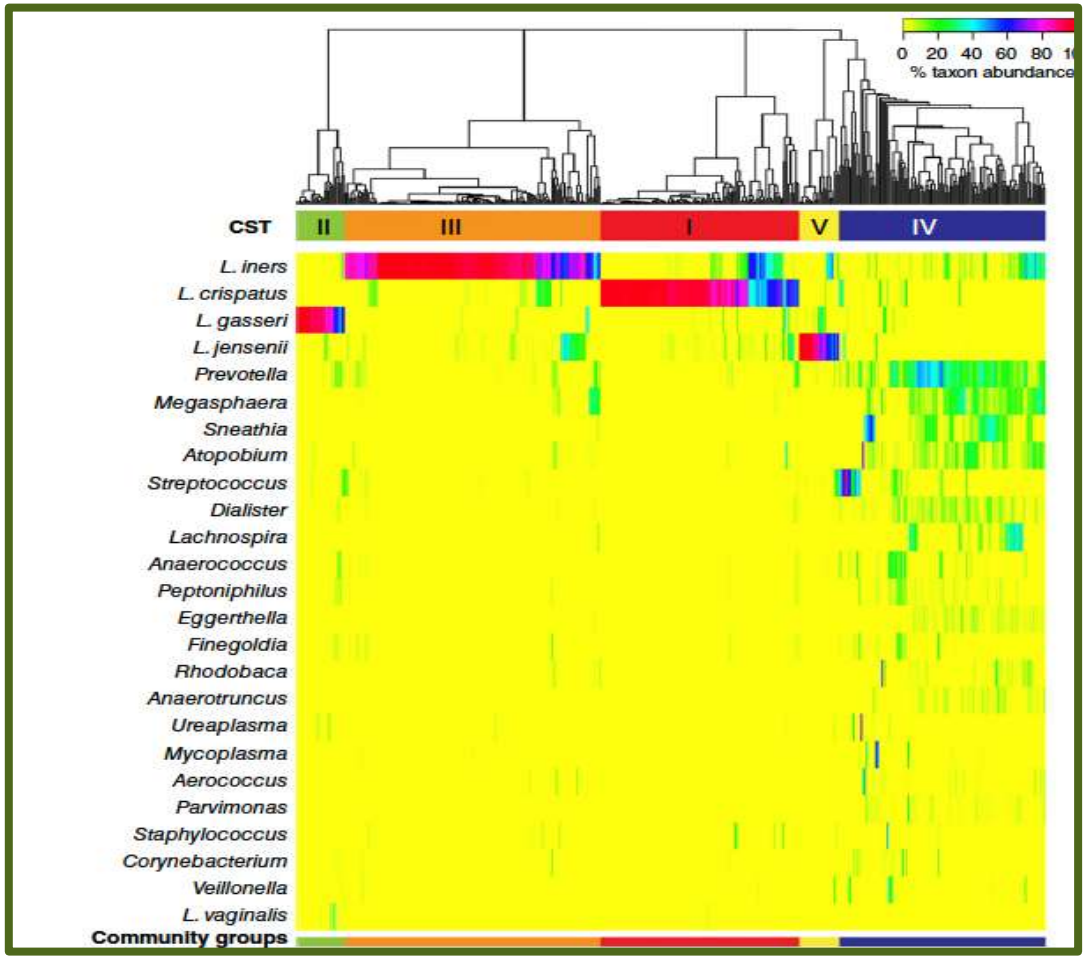
. P. Lepargneur et al. - *J. Gynecol. Biol. Reprod., 31: 485-494,2002*

Vaginal Microbioma

Four of these CSTs are dominated by lactobacilli species

- **CST-I** L. crispatus
- **CST-II** L. gasseri
- **CST-III** L. Iners
- **CST-V** L. jensenii

CST-IV *is composed of a polymicrobial mixture of strict and facultative* ***anaerobes*** *including species of the genera* ***Gardnerella, Atopobium,Mobiluncus, Prevotella*** *and other taxa in the order* ***Clostridiales***



(Fredricks et al. 2005; Campos et al. 2008; Ravel et al. 2011; Gajer et al. 2012).

TIPOLOGIE DI COMUNITA'

Community state types (CST) in the vaginal microbiota.[a]

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].

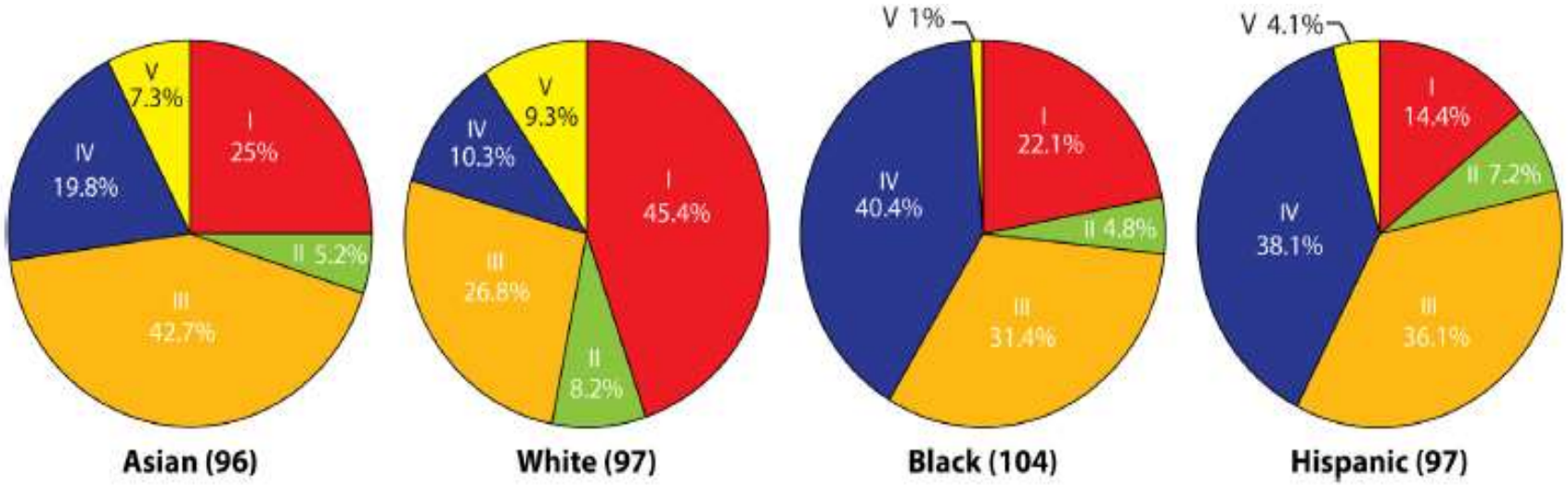
Microbiome, sex hormones, and immune responses in the reproductive tract: Challenges for vaccine development against sexually transmitted infections

Rebecca M. Brotman[a,b,*], Jacques Ravel[a,c], Patrik M. Bavoil[d], Patti E. Gravitt[e], Khalil G. Ghanem[f,**]

Vaccine 2014 (32) 1543-1552

Non tutte le comunita'
dominate dai lattobacilli

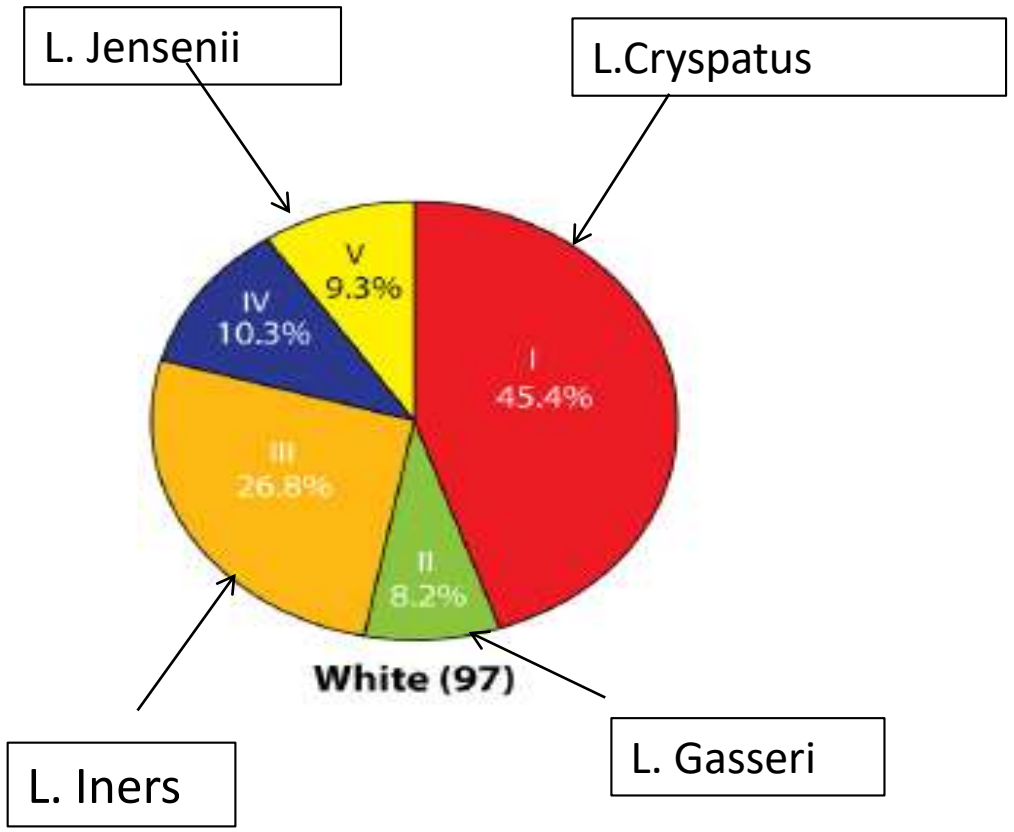
Differenze etniche



GYNECOLOGIC HEALTH AND DISEASE IN RELATION TO THE MICROBIOME OF THE FEMALE REPRODUCTIVE TRACT

Katherine A. Green,
Fertility and Sterility 2015

VAGINAL MICROBIOME IN THE HEALTHY STATE.



- Most frequently detected

Lactobacillus iners, Lactobacillus crispatus, Lactobacillus gasseri, Lactobacillus jensenii

- However, a portion OF **ASYMPTOMATIC, HEALTHY WOMEN,** particularly black and Hispanic women, **host a polymicrobial vaginal** environment dominated by bacteria other than Lactobacilli, including **Prevotella, Gardnerella, Atopobium, and Megasphaera species**

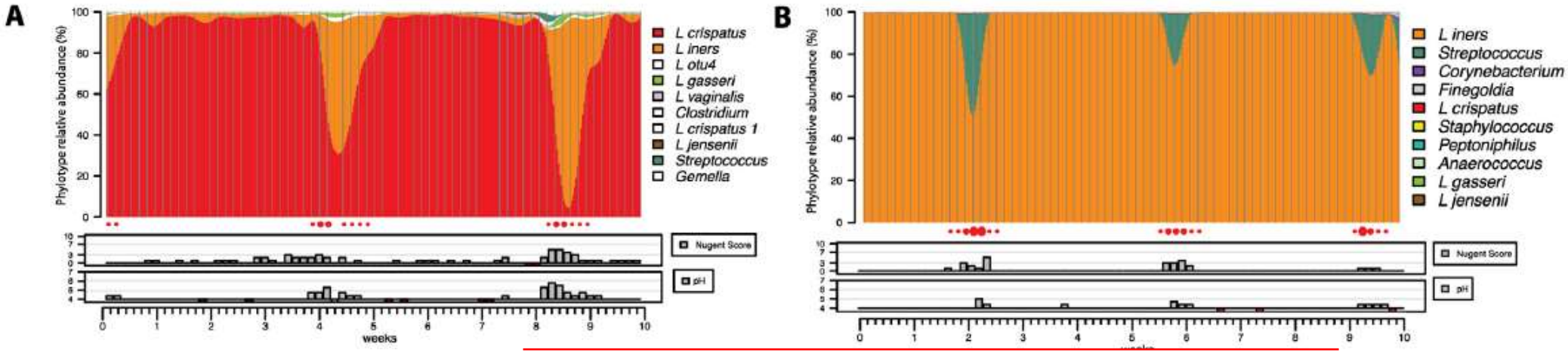
Normal vaginal microbiome is **dominated by Lactobacilli species**

DINAMICHE TEMPORALI DIURNE delle comunita' di batteri vaginali in 4 donne durante un periodo di 10 settimane

Vaccine 2014 (32) 1543-1552

STABLE and UNSTABLE CTS

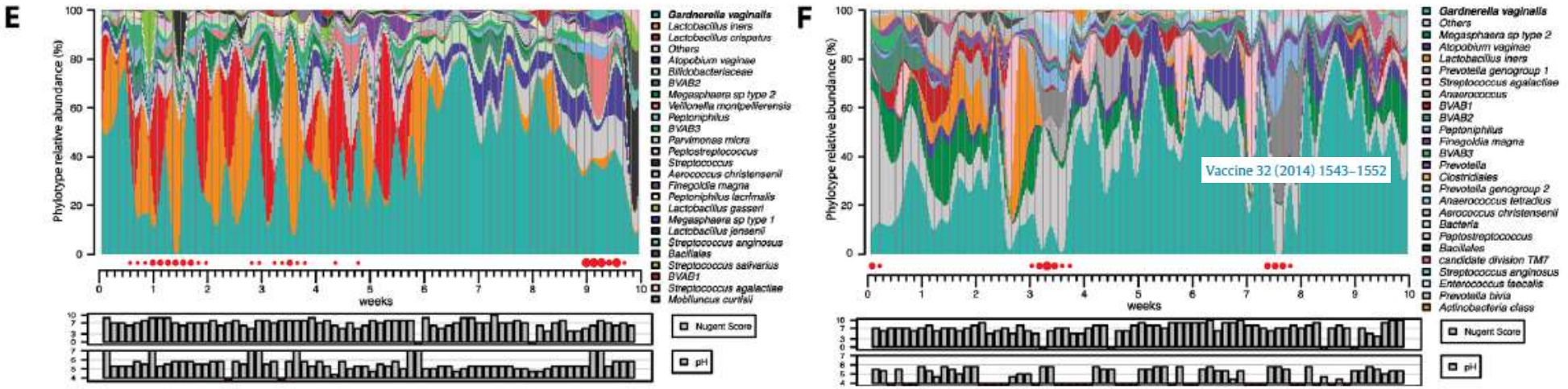
Stable Community State Type



A: tipo1
B: tipo 3

Comunita' dominata da lattobacilli (Crispatus/Iners)

Unstable Community State Type

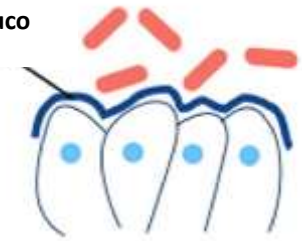


E: tipo 4B
F: tipo 4B

Comunita' instabili con alto grado di Nugent Score e PH

Microbiota vaginale sano a dominanza lattobacillare

Strato di muco



25%

CST I
L. crispatus

5%

CST II
L. gasseri

5%

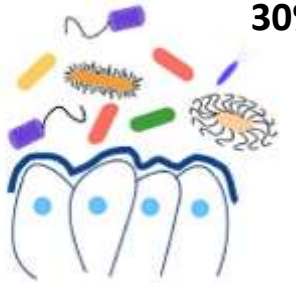
CST V
L. jensenii

Evoluzione verso eubiosi

Microbiota vaginale sano/disbiotico in fase di transizione

35%

CST III
L. iners



30%

CST IV-A
No lattobacilli

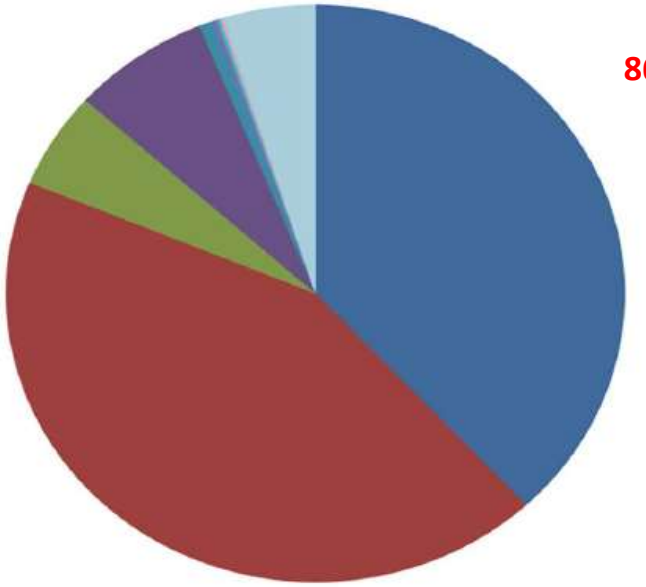
Evoluzione verso vaginosi

Evoluzione verso vaginosi

Microbiota vaginale disbiotico con vaginosi

CST IV-B
No lattobacilli

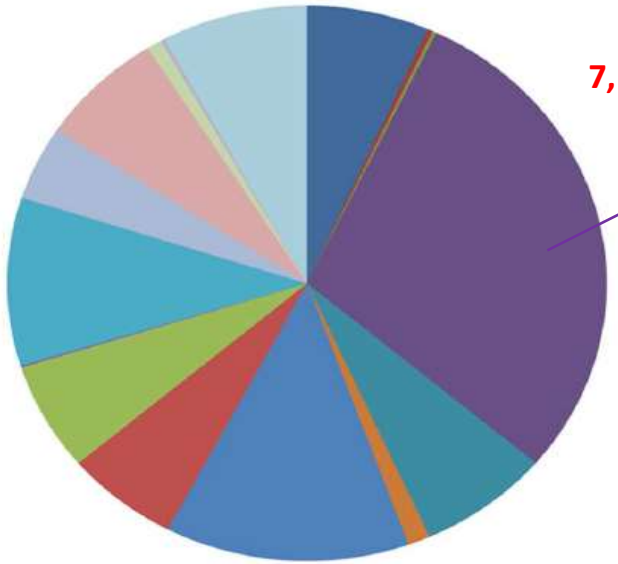
Controls



86,7%

- Lactobacillus iners (38.1%)
- Lactobacillus crispatus (43.2%)
- Other Lactobacillus species (5.4%)
- Gardnerella vaginalis (7.2%)
- Atopobium vaginae (0.6%)
- Eggerthella (0.001%)
- Prevotella (0.2%)
- BVAB 1 (0.02%)
- BVAB 2 (0.01%)
- Finegoldia magna (0.1%)
- Megasphaera type 1 (0.2%)
- Megasphaera type 2 (0%)
- Sneathia sanguinegens (0.1%)
- Leptotrichia amnionii (0.1%)
- BVAB-TM7 (0.002%)
- Mobiluncus curtisii/mulieris (0.002%)
- Other non-Lactobacillus species (4.8%)

BV



7,1%

- Lactobacillus iners (6.6%)
- L. crispatus (0.3%)
- Other Lactobacillus species (0.2%)
- Gardnerella vaginalis (29.1%)
- Atopobium vaginae (7.1%)
- Eggerthella (1.2%)
- Prevotella (13.2%)
- BVAB 1 (6.1%)
- BVAB 2 (6.3%)
- Finegoldia magna (0.1%)
- Megasphaera type 1 (9.8%)
- Megasphaera type 2 (0.1%)
- Sneathia sanguinegens (4.3%)
- Leptotrichia amnionii (6.8%)
- BVAB-TM7 (0.8%)
- Mobiluncus curtisii/mulieris (0.2%)
- Other non-Lactobacillus species (7.9%)

Plos One 2013

OPEN ACCESS Freely available online

Composition of the Vaginal Microbiota in Women of Reproductive Age – Sensitive and Specific Molecular Diagnosis of Bacterial Vaginosis Is Possible?

Elena Shipitsyna[1], Annika Roos[2], Raluca Datcu[3], Anders Hallén[4], Hans Fredlund[3], Jørgen S. Jensen[3], Lars Engstrand[2], Magnus Unemo[3]*

- La presenza di Gardnerella/ Atopium /BVAB2/ Megasfera tipo 1
- Deplezione Lattobacilli (CST IVB)

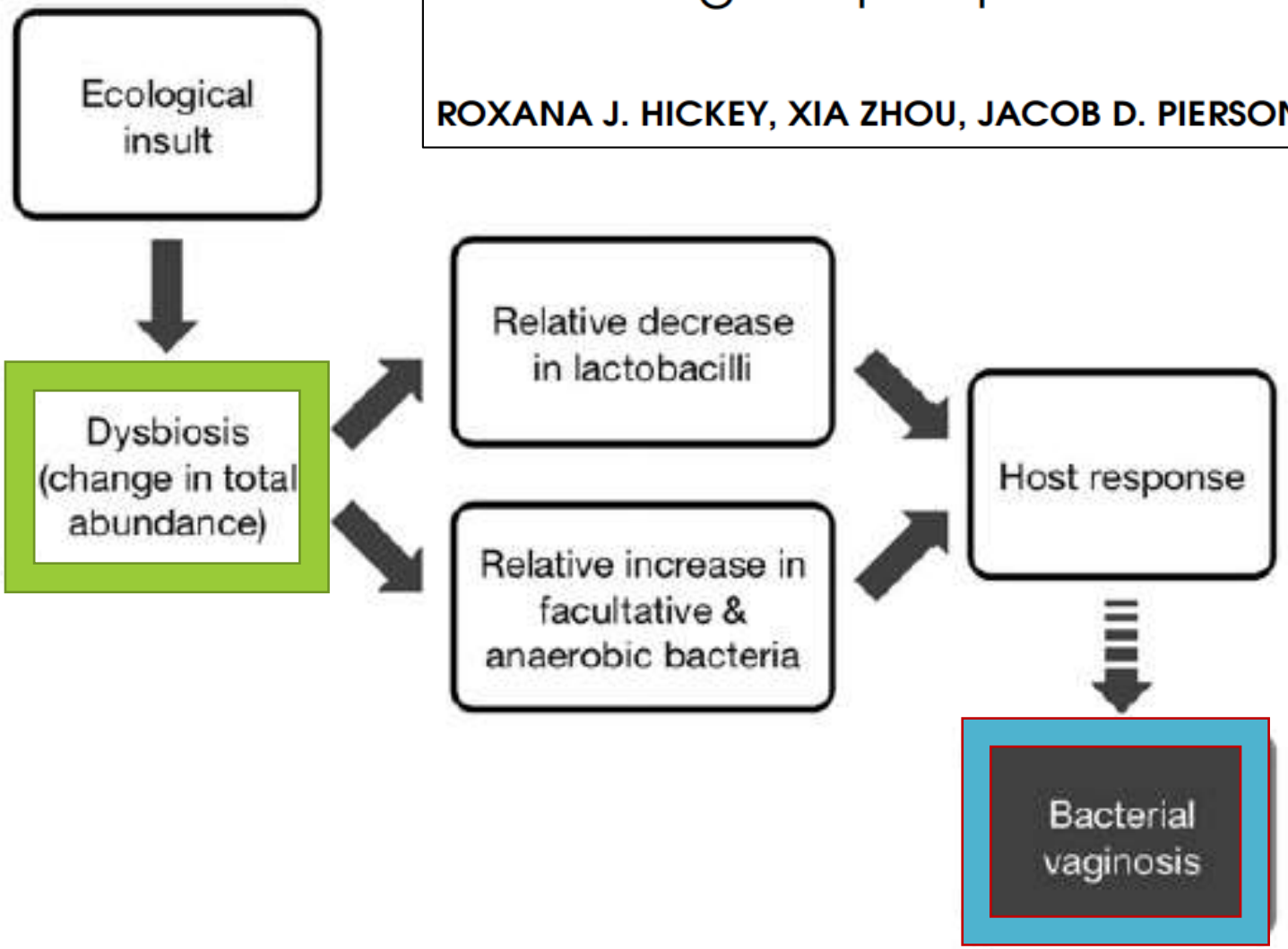
Correla con diagnosi di vaginosi batterica

VAGINOSI BATTERICHE VB

Understanding vaginal microbiome complexity from an ecological perspective

Translational Res 2012

ROXANA J. HICKEY, XIA ZHOU, JACOB D. PIERSON, JACQUES RAVEL, and LARRY J. FORNEY



- Patologie ginecologiche
  - vaginosi ricorrenti
  - cerviciti
  - endometriti, P.I.D.
  - infezioni postchirurgiche
  - U.T.I.

IMPORTANZA DEI LATTOBACILLI A LIVELLO VAGINALE

MANTENIMENTO pH ACIDO

Fermentano il glicogeno a idrogenioni H+ con produzione di acido lattico e altri acidi grassi

<< ph vaginale (4 - 4.5)

PRODUZIONE H_2O_2

Gli idrogenioni H+ e H_2O producono **PEROSSIDO DI IDROGENO** ad effetto battericida verso molti batteri, soprattutto anaerobi e con proprietà ossidanti

STIMOLAZIONE DELL'ATTIVITA' DELL'ARGININA-DEAMINASI

Questo enzima **distrugge le POLIAMINE,** responsabili dei sintomi clinici della VB

PRODUZIONE BATTERIOCINE

Alcuni lattobacilli sono in grado di produrre
BATTERIOCINE E SOST. BATTERIOCINO-SIMILI:

sono sostanze proteiche in grado di produrre
EFFETTI ANTAGONISTICI FRA LE SPECIE MICROBICHE
e che possono **INIBIRE LA REPLICAZIONE**
di molte specie fungine
e di molti batteri GRAM+ e GRAM-

Vaginal microbiota before and after menopause

MENOPAUSE IS FOLLOWED BY VAGINAL MICROBIOME CHANGES

↓ LB speceis

↑ Vaginal PH

→ increased infections and worsens VVA symptoms

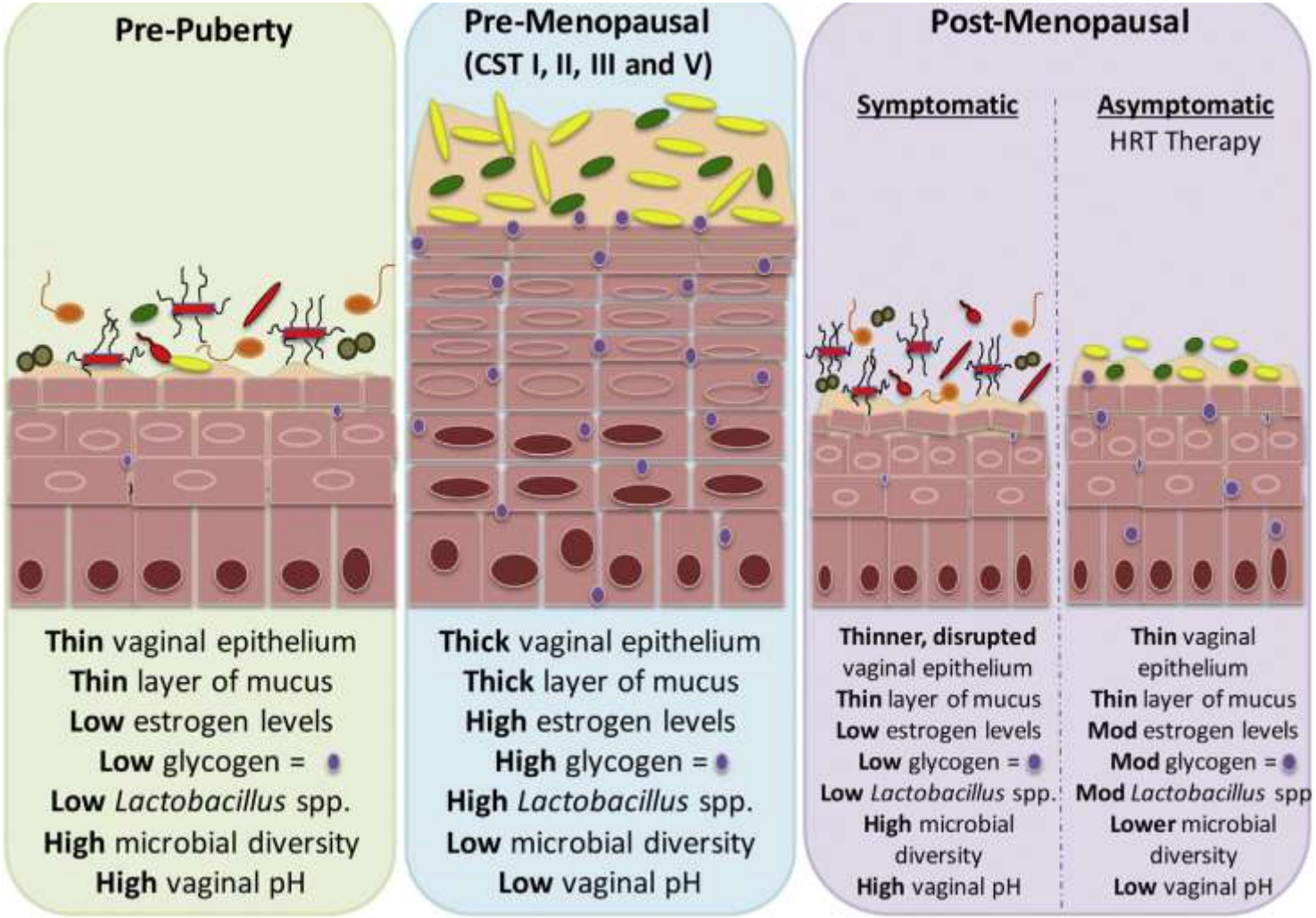
(Hillier and Lau, 1997; Brotman et al., 2014; Shen et al., 2016)

Few studies showed a similar vaginal microbiome composition in women taking HRT compared with premenopausal women.

(Mitchell et al., 2017, Yoshimura and Okamura, 2001; Heinemann and Reid, 2005; Shen et al., 2016; Mitchell et al., 2017).

Vaginal microbiome and MENOPAUSE

The vaginal microbiome changes dramatically across the female lifespan concurrent with hormonal and microanatomical features of the vaginal epithelium

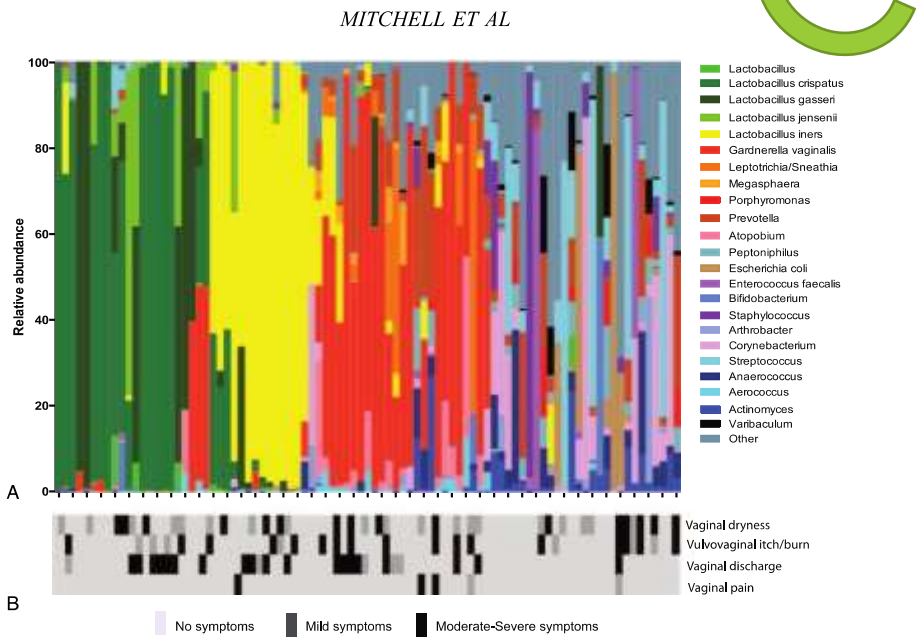


Following menopause the levels of estrogen drop, decreasing glycogen and the vaginal epithelium resembles the pre-puberty stage, with less layers and a thinner mucus layer. In some cases, this leads to depletion of Lactobacillus spp. and an increase in diverse microbial species and community states (CST IV-A and CST IV-B), which has a higher association with vaginal symptoms

Vaginal microbiome and MENOPAUSE

- **LACTOBACILLI WERE PROMINENT members of vaginal communities of most healthy post-menopausal women.**

Menopause, Vol. 24, No. 10, 2017



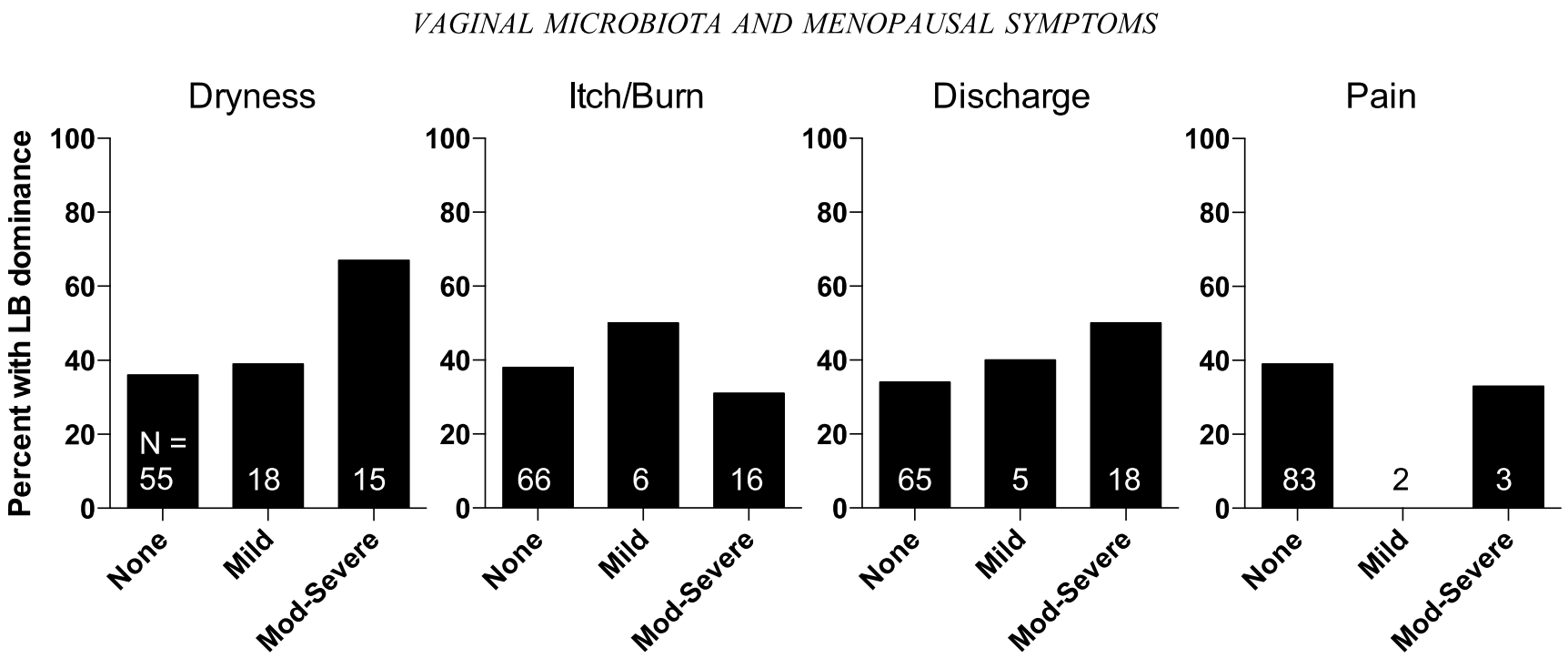
- **Contrary to the common wisdom that *Lactobacillus* spp. are usually absent from the vaginal microbiome in menopause, we found that …..**

- Communities of cluster I were most common and present in 50.6% of the samples.These communities were dominated by *Lactobacillus* that constituted >50%
- Communities of cluster II were present in 10.3% of the samples and had high proportions of *Prevotella*, *Atopobium*, *Streptococcus* or *Gardnerella*

FIG. 1. (**A**) Relative abundance of the most common vaginal bacteria among 88 postmenopausal women, as determined by 16S rRNA gene sequencing. (**B**) Presence and severity of patient-reported vulvovaginal symptoms.

Vaginal microbiome and MENOPAUSE

Menopause, Vol. 24, No. 10, 2017

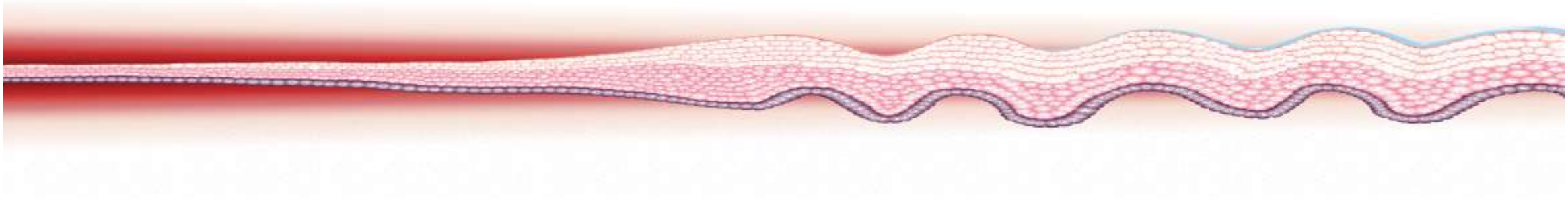


Lactobacillus dominance was not associated with severity of individual symptoms

FIG. 2. Proportion of women with *Lactobacillus*-dominant vaginal communities (more than 50% of sequences from *Lactobacillus* spp.) with no, mild, or moderate-to-severe symptoms. Numbers in the bars are the number of participants reporting that severity of symptom. No significant differences were noted in *Lactobacillus* dominance according to symptom severity for any of the symptoms.

Vaginal microbiome and MENOPAUSE VAGINAL ATROPHY

Decreased Lactobacilli, particularly L. crispatus, as well as increased bacterial diversity and instability, have been observed in postmenopausal women, specifically those with vaginal dryness or atrophy



Healty postmenopausal women / Postmenopausal women with Vaginal atrophy

SCIENTIFIC REPORTS
2016

PHYLOTYPE ABUNDANCE

Phylotype relative abundances in four selected subjects in the AV group over 4 weeks

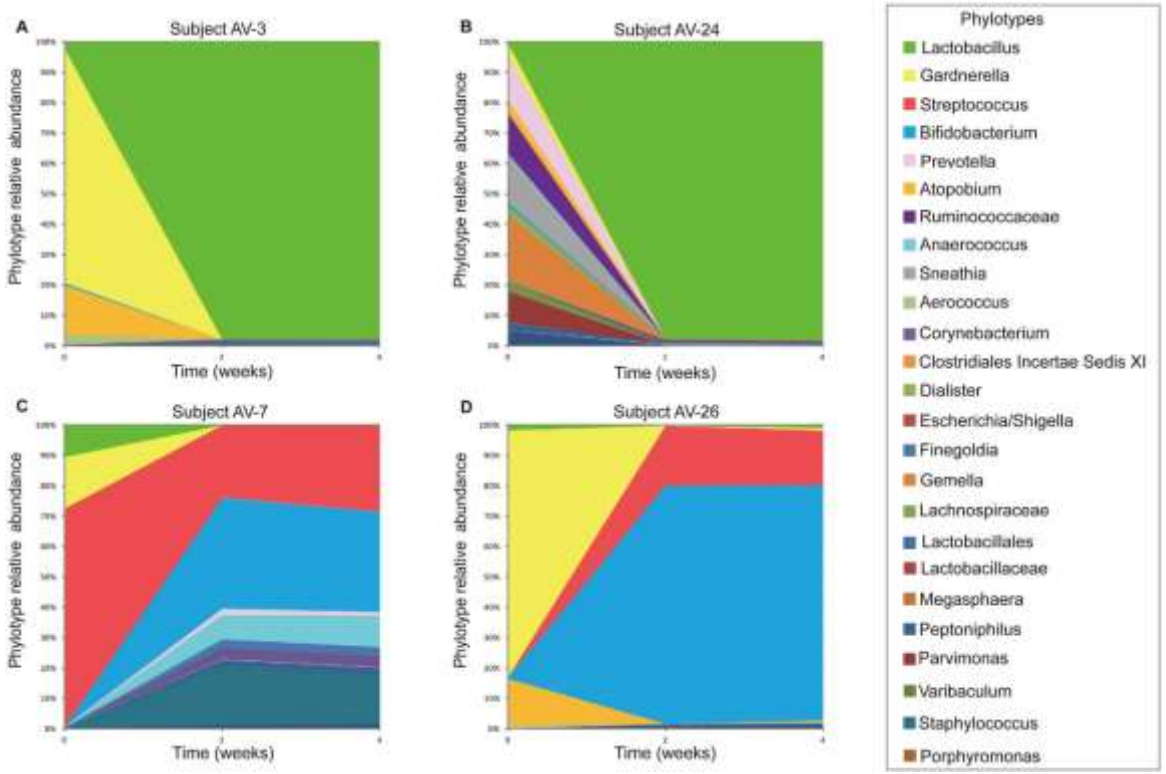


Figure 5. Interpolated bar plots of phylotype relative abundance observed in four subjects selected from the AV group. Color codes for each phylotype represented in the interpolated bar plots are displayed on the right side of the figure. See Supplementary Fig. S2 interpolated bar plots for all subjects.

ATROPHY

Phylotype relative abundances in four selected subjects in the H group over 4 weeks

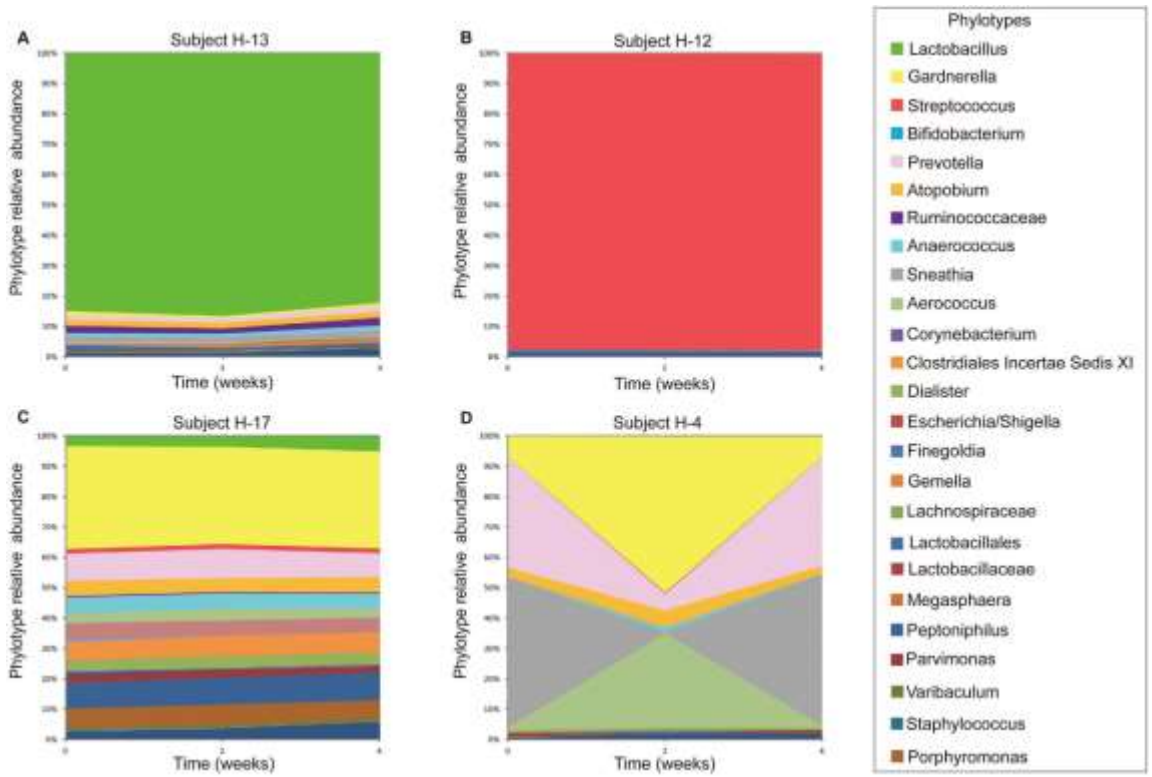


Figure 2. Interpolated bar plots of phylotype relative abundances in four selected subjects in the H group over 4 weeks (panels **A–D**). Color key for each phylotype represented in the interpolated bar plots are on the right side.

HEALTY

EFFECTS OF LOW DOSE ESTROGEN THERAPY ON THE VAGINAL MICROBIOMES OF WOMEN WITH ATROPHIC VAGINITIS

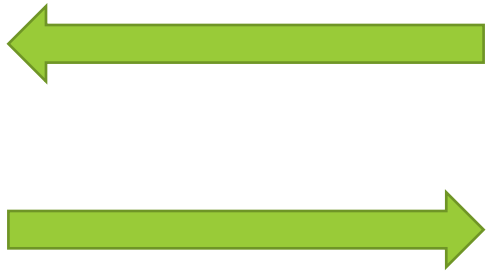
SCIENTIFIC REPORTS
Jian Shen 2016
www.nature.com/scientificreports

The changes in community composition in response to hormonal therapy were rapid and typied by

signicant increases in the relative abundance of Lactobacillus

That were mirrored by a **decreased relative abundance of Gardnerella**

LOW dose HT

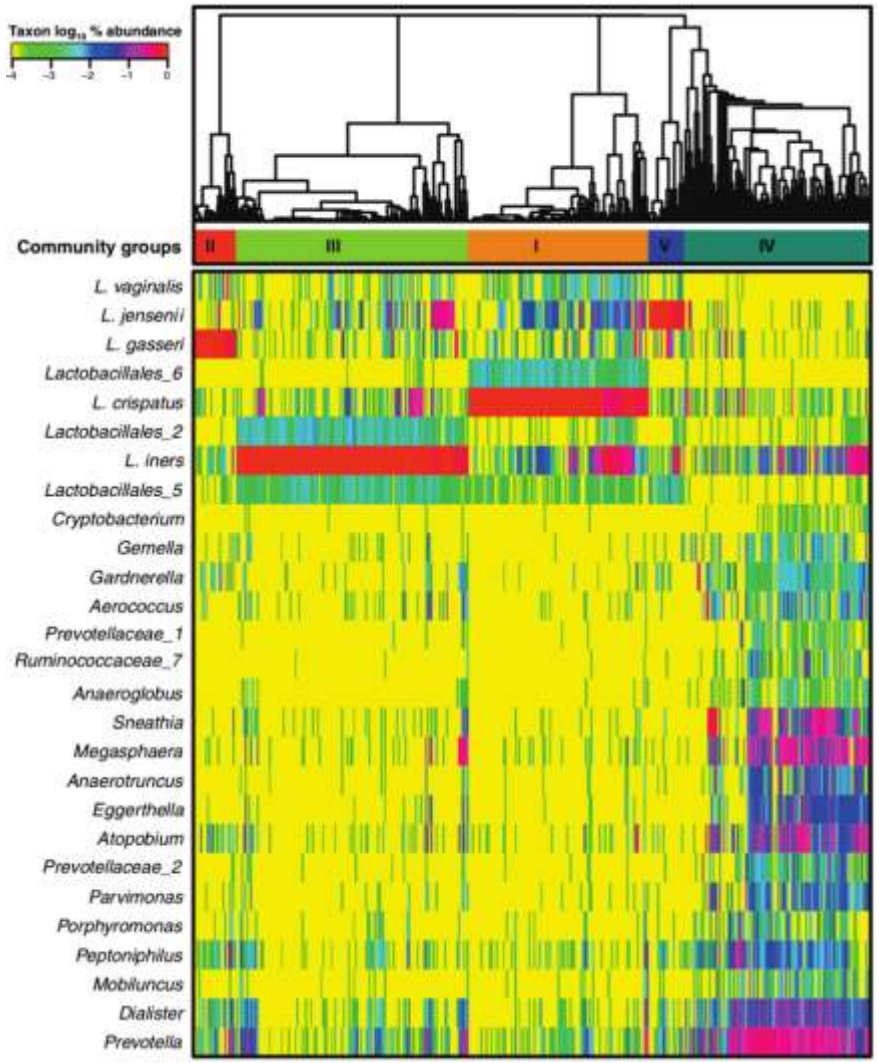


These changes were paralleled by a **signicant four-fold increase in serum estradiol levels and decreased vaginal pH**

as well as nearly a two-fold increase in the Vaginal Maturation Index

CONCLUSIONI I

- Diverse tipologie di valutazione del microbiota
  - Microbiota con **prevalenza di LB è maggiormente associato alla salute vaginale**
  - Caratterizzazione genica del microbioma ha evidenziato una **complessita'** ancora da definire
  - Disbiosi come classicamente definita **PUO' ESSERE** o **NO** associata a vaginosi batterica
- **Non sempre** la disbiosi e' sintomatica



CONCLUSIONI II

Utilizzo di prebiotici e probiotici :

- ✓ Trattamento delle disbiosi sintomatiche e prevenzione delle infezioni
- ✓ In associazione alle terapie antibiotiche
- ✓ Utilizzo di terapie ormonali o non ormonali della menopausa e probiotici nella sindrome genitourinaria
- ✓ Interventi in prevenzione delle disbiosi per **ripristinare o mantenere la flora batterica dominante e per la prevenzione di patologie mediche postmenopausali**