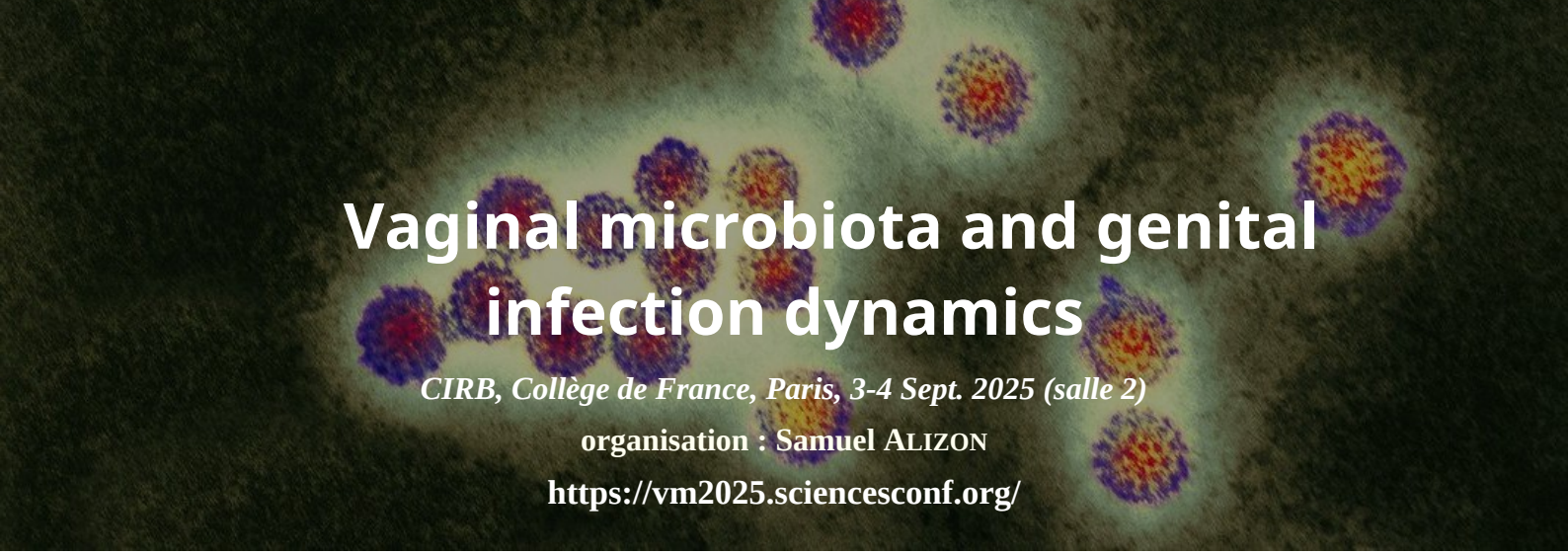

Vaginal microbiota and genital infection dynamics

CIRB, Collège de France, Paris, 3-4 Sept. 2025 (salle 2)

organisation : Samuel ALIZON

https://vm2025.sciencesconf.org/

Wednesday, September 3rd, 2025

13h45: Welcome in Salle 2

- 14h: **Nicola LOW** (Institute of Social and Preventive Medicine, Berne, Switzerland) *Vaginal dysbiosis during pregnancy and associations with gestational age at birth: findings from the Philani Ndiphile cohort study among pregnant women in South Africa*
- 14h50: **Louis COLLIOT** (CIRB, Paris) *Modelling the HIV epidemic in France using virus genomic data*
- 15h10: **Inayat BHARDWAJ** (MIVEGEC, Montpellier) *Host Adaptive Immunity Shapes Asymptomatic HPV Clearance*

15h30: coffee/tea break in room Glowinski

- 16h: **Thomas BÉNÉTEAU** (IAME, Paris) *On the use of Tecovirimat for MPXV infections: why does it not work?*
- 16h30: **Julia GNÄGI** (University of Applied Sciences and Arts Northwestern Switzerland) *qPCR-based quantification of Gardnerella spp. in vaginal and penile samples: insights into partner dynamics*
- 16h50: **Mathias CARRIOU** (CIRI, Lyon) Candida albicans *promotes TSST-1 production in* Staphylococcus aureus *by depleting glucose and lifting CcpA-mediated repression of the tst gene*
- 17h10: **Alessandra CERVINO** (Pileje, France)

17h30: end of day 1

Thursday, September 4th 2025

9h15: Welcome in Salle 2

- 9h30: **Janneke VAN DE WIJGERT** (Utrecht Medical Center, The Netherlands) *The effects of Depo Provera and norethisterone enanthate injectable contraceptives on the vaginal microbiome of women at a high risk for HIV infection in Kampala, Uganda*
- 10h20: **Asmaa TAZI** (Institut Cochin, Paris) *Vaginal microbiota and pregnancy outcomes: a prospective cohort study of a high-risk population for preterm birth and neonatal infections.*
- 11h10: **Anaïs BLACHE** (MIVEGEC, Montpellier) *Menstrual products as disruptors of host-microbiota interactions ?*

11h30: coffee break in room Glowinski

- 12h00: **Sean KENNEDY** (Institut Pasteur, Paris) *The Vaginal Microbiota during Pregnancy: Structured Resistomes and Strain-Level Genomics*
- 12h30: **Elita JAUNEIKAITE** (Imperial College, London) *Pathogen Genomics in Maternal and Neonatal Health: understanding the vaccine targets and mother-to-baby transmission of Group B streptococcus*

13h30: lunch break

- 15h00: **Jacques RAVEL** (Institute for Genomic Sciences, University of Maryland, USA) *Translating our ecological understanding of the vaginal microbiome into novel live biotherapeutic products*
- 15h50: **Tomas FREIRE** (Instituto Superior Tecnico, University of Lisbon) *Modeling the vaginal microbiome and its protection against pathogens using the replicator framework for invasion -*
- 16h20: **Yusheng WANG** (Antwerp University) *Exploring Alternative Metabolism in Lactobacilli for Increased Fitness within the Vaginal Ecosystem*

16h40: coffee/tea break in room Glowinski

- 17h10: **Quentin CHAUNG** (CIRB, Paris) *Within-host community dynamics of the vaginal microbiota in young adult women*
- 17h40: **Alice GALLOT** (ENS, Paris) *Uncovering the Evolutionary and Ecological Landscape of Vaginal Prevotella through Genomic Comparisons*

18h00: end of the meeting

The meeting is sponsored by the Collège de France, the Action Coordonnée Modélisation of the ANRS-MIE and the PSL Global Seed Fund from Université PSL

Modelling the HIV epidemic in France using virus genomic data

Louis Colliot*[1], Samuel Alizon[2], and Laurence Meyer

[1]CIRB, Collège de France – Université PSL, CNRS, INSERM, 75005 Paris, France, – France
[2]Centre interdisciplinaire de recherche en biologie (CIRB) – Collège de France, Institut National de la Santé et de la Recherche Médicale, Centre National de la Recherche Scientifique, Université de recherche Paris Sciences Lettres (PSL) – 11 place Marcelin Berthelot, 75005 Paris, France

Résumé

Every time the Human Immunodeficiency Virus (HIV) replicates within a cell, errors can creep into its genome. These mutations make it possible to track an epidemic, because the more similar two virus sequences are, the closer the two individuals who bear them are likely to be in the chain of transmission.
For more than twenty years, the field of phylodynamics has been analyzing this type of data to estimate, for example, epidemic growth rates or dispersion rates between regions. The SARS-CoV-2 pandemic illustrated the power of these methods, which remain marginal in France where routine sequencing performed during HIV screening is rarely used for epidemiological surveillance. However, this method is adapted to this epidemic, it could inform us about the presence of clusters or the scale of the 'hidden' epidemic, which, by definition, is difficult to estimate because it is not screened. Thanks to the collaboration with leading national clinical virology teams, we analyze data from French cohorts, namely the national PRIMO cohort. Preliminary results allow us to place the French epidemic in a global context and to successfully characterize homogeneous clades for the most common circulating subtype (HIV1-B). This better understanding of the structure of the French HIV epidemic will help guide future phylodynamic analyses to estimate dynamics variations in overexposed populations over time. In particular, we will focus on assessing the proportion of the epidemic that is hidden to optimize public health policies.

*Intervenant

Host Adaptive Immunity Shapes Asymptomatic HPV Clearance

Inayat Bhardwaj*[1], Vanina Bouté[1], Ignacio Bravo[1], Samuel Alizon[2], and Nicolas Tessandier[1]

[1]Virostyle – Perturbations, Evolution, Virulence – France
[2]Centre interdisciplinaire de recherche en biologie – Labex MemoLife, Collège de France, Institut National de la Santé et de la Recherche Médicale, Centre National de la Recherche Scientifique – France

Résumé

Human papillomaviruses (HPVs) are among the most prevalent sexually transmitted infections and a major etiological factor in cervical cancer. More than 80% of cervical cases are caused by persistent infection with oncogenic HPV, with types 16 and 18 accounting for approximately 75% of cases. Although most HPV infections clear spontaneously within two years, persistent oncogenic infections can lead to high-grade precancerous lesions and, if untreated, invasive cervical cancer. Despite this, the host factors that enable spontaneous viral clearance are still poorly understood. In this study, we used bulk RNA sequencing data from cervical samples (n=100) from the PAPCLEAR clinical cohort to identify host transcriptomic signatures that distinguish individuals who clear asymptomatic HPV infections. Post-sample pre-processing, differential expression was assessed for samples that passed the quality assessment (n=71). Gene set enrichment analysis (GSEA) was used to identify significantly enriched biological pathways. Based on our data, HPV16-dominated infections showed upregulation of innate antiviral pathways, including type I interferon signaling. Furthermore, non-clearing infections exhibited activation of adaptive immune response, including pathways based on recombination of immune receptors built from immunoglobulin domains and downregulation of keratinocyte differentiation pathways. Strikingly, infections lasting for the longest duration were marked by negative enrichment of pathways related to tumor necrosis factor (TNF) production and regulation, leukocyte activation, and a positive enhancement of B-cell and immunoglobulin-mediated adaptive immune responses. Our analyses of host transcriptomic data from asymptomatic infections suggest that adaptive immunity is the most prominent factor distinguishing non-clearing infections.

*Intervenant

On the use of Tecovirimat for MPXV infections: why does it not work?

Thomas Beneteau*[1]

[1]IAME - Université Paris Cité, INSERM – Hôpital Bichat - Claude Bernard – France

Résumé

In 2022, the mpox virus (MPXV) was declared a Public Health Emergency of International Concern (PHEIC) by the World Health Organization following a global outbreak of clade IIb. In 2024, MPXV was again declared a PHEIC after a resurgence of clade Ib in Central Africa, particularly in the Democratic Republic of Congo. Tecovirimat, an antiviral targeting orthopoxviruses, was approved for smallpox treatment prior to the 2022 outbreak, based on animal efficacy data and safety studies in healthy individuals and was considered as the primary candidate for mpox treatment.
Following the 2022 outbreak, three clinical trials were launched to assess Tecovirimat's efficacy in humans. Early results from two studies showed the treatment was safe but did not reduce the time to lesions resolution nor shorten the duration of the viral presence in biological samples. These findings were unexpected, as Tecovirimat has demonstrated nanomolar *in vitro* efficacy against multiple MPXV clades, supported by studies in non-human primates and mice models.
In this study, we used a non-linear mixed effects modelling approach to assess the impact of delayed treatment initiation and suboptimal drug exposure on the time to viral clearance between treated and untreated participants. Our results suggests that, even with delayed treatment and/or under suboptimal dosage regimen, a significant difference in the time to viral clearance between treated and untreated individuals should be observed even 14 days after inclusion. More generally, our findings point to additional factors not captured by the current model that may contribute to the apparent lack of antiviral efficacy on the time to viral clearance observed in the clinical studies so far such as a poor diffusion of the drug to the targeted compartments or the emergence of tecovirimat-resistant MPXV strains.

*Intervenant

qPCR-based quantification of Gardnerella spp. in vaginal and penile samples: insights into partner dynamics

Julia Gnägi*[1], Hanna Marti[2], Marcel Suleiman[1], Enrique Rayo[2], Natasha Arora[3], and Monica Ticlla Ccenhua[4]

[1]Fachhochschule Nordwestschweiz [Windisch, Schweiz] = FHNW University of Applied Sciences and Arts Northwestern Switzerland – Suisse

[2]Institute of Veterinary Pathology, University of Zurich – Suisse

[3]Zürich Institute of Forensic Medicine, University of Zürich, Zürich – Suisse

[4]Swiss Tropical and Public Health Institute [Basel] – Suisse

Résumé

Gardnerella spp. is a natural bacterial component of the vaginal microbiome. However, its overabundance is linked to bacterial vaginosis (BV), a shift in the vaginal microbial environment associated with an increased risk of infertility, perinatal complications and sexually transmitted infections (STI). Although BV is not currently classified as an STI, *Gardnerella spp.* has been detected in the penile anatomy. Reliable detection of *Gardnerella spp.* in vaginal and penile samples is therefore crucial for understanding its potential transmission dynamics, the role of male partners in BV onset and recurrence, and its broader implications for sexual health. We implemented and validated a quantitative polymerase chain reaction (qPCR) assay targeting the *elongation factor Tu* gene of *Gardnerella spp.* We applied this method to 163 vaginal fluid and penile skin samples from 22 heterosexual couples in Switzerland. This is intended to explore potential links between microbial patterns and factors such as partner dynamics, sexual practices, e.g. use of barrier contraceptives, and broader questions around the transmission and classification of *Gardnerella spp.* as a sexually associated pathogen. Our results show low to moderate positive correlations of *Gardnerella spp.* loads between sexual partners samples across three timepoints (Spearman's $\rho = 0.38, 0.76, 0.51$). No association was found between bacterial load and frequency of sexual intercourse. Condom use was linked to significantly lower *Gardnerella spp.* loads in penile skin samples, but not in vaginal fluid. Improved understanding of these patterns may support more effective treatment strategies and reduce stigma surrounding vaginal and sexual health by making this knowledge more accessible to the public.

*Intervenant

Candida albicans promotes TSST-1 production in Staphylococcus aureus by depleting glucose and lifting CcpA-mediated repression of the tst gene

Mathias Carriou*[1], Cédric Badiou[1], Alexandre Soulard[2], Karine Dufresne[3], and Gérard Lina[4,5,6]

[1]International Research Center on Infectious diseases (CIRI) – INSERM U1111 – CNRS UMR5308 – Université Claude Bernard - Lyon I, CNRS, Institut National de la Santé et de la Recherche Médicale - INSERM, École normale supérieure - Lyon (ENS Lyon) – France

[2]Laboratoire Microbiologie, Pathogénie, Adaptation – Université Claude Bernard - Lyon I, CNRS, INSA Lyon, France – France

[3]Université du Québec à Montréal – UQAM - Université du Québec à Montréal – France

[4]Université Claude Bernard Lyon 1 (UCBL) – Université de Lyon, Université Lyon 1 – 43, boulevard du 11 novembre 1918, 69622 Villeurbanne cedex, France

[5]Hospices Civils de Lyon, Institut des Agents Infectieux – Hospices Civils de Lyon – France

[6]CIRI, International Center for Infectiology Research, Lyon, France – CIRI, Inserm, U1111, Université Claude Bernard Lyon 1, CNRS, UMR5308, École Normale Supérieure de Lyon, Univ Lyon, F-69007, Lyon, France – France

Résumé

During menstruation, the gram-positive opportunistic pathogen *Staphylococcus aureus* can cause menstrual toxic shock syndrome (mTSS), a rare yet life-threatening disease, through the release of the superantigen TSST-1 (toxic shock syndrome toxin 1). Prolonged use of intravaginal menstrual products has been the main risk factor for mTSS, facilitating *S. aureus* growth in menstrual blood and TSST-1 production (Schlievert & Davis, 2020). However, various studies suggest the potential role of vaginal microbiota in mTSS development, including yeasts such as *Candida albicans* (Jacquemond et al., 2018; MacPhee et al., 2013; Maduta et al., 2024). Thus, this study investigated the potential role of vaginal *Candida* species, especially *C. albicans*, in the stimulation of TSST-1 production of *S. aureus*, through increased glucose depletion and relieving of CcpA-mediated gene repression.
Wild-type and slow glucose-depleting *C. albicans* strains were cultivated at 37∘C for up to 18h in Brain Heart Infusion, supplemented or not with glucose. Culture supernatants were mixed with *S. aureus* suspensions and incubated for 6h at 37∘C. TSST-1 levels were quantified by ELISA following exposure to fungal supernatant or control medium.

TSST-1 production was negatively correlated with glucose levels in both control medium and *C. albicans* supernatants. Limiting yeast glucose depletion delayed downstream TSST-1 production; glucose supplementation of supernatants inhibited toxin production of *S. aureus*. Deletion of the glucose-responsive regulator CcpA lead to increased TSST-1 production, independently of glucose levels in medium and supernatants. Furthermore, deletion of the

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exotoxin regulator SaeRS abolished TSST-1 production entirely.
In conclusion, CcpA inhibits TSST-1 production in high glucose conditions. Then, glucose depletion in medium by *C. albicans* during its growth, which lifts this repression, enabling SaeRS-mediated production of TSST-1 by S. aureus. These results highlight the importance of interkingdom microbial interactions and glucose availability in the regulation of *S. aureus* virulence and mTSS development.

Menstrual products as disruptors of host-microbiota interactions ?

Anaïs Blache*[1], Lïam Cousin[2], Alicia Calistri[3], and Nicolas Tessandier[3]

[1]MIVEGEC – CNRS-IRD-Université de Montpellier – France
[2]MIVEGEC – CNRS-IRD-Université de Montpellier – France
[3]MIVEGEC – CNRS-IRD-Université de Montpellier – France

Résumé

Vaginal microbiota exerts a major influence on women's health. Host-microbiota interactions and bacterial communities composition are intricately linked to vaginal health. A vaginal microbiota dominated by single species of *Lactobacillus*, has beneficial effects on host cells. In contrast, *Lactobacillus*-poor microbiota is associated with an increased risk of sexually transmitted infections (eg: HIV, HPV) and preterm birth. Availability, efficiency, and safety of menstrual products are key to women's health. Poor menstrual health management can have deleterious consequences, from decreasing school attendance to increasing the risk of urogenital infections and bacterial vaginosis. In France and in the EU menstrual products are considered as hygiene products. They are therefore not subject to strict composition restrictions and are exempt from post-commercialisation safety assessments. This study investigates the influence of pollutants detected in internal menstrual products on both key vaginal bacterial species and on vaginal cells.
The impact of chemicals presents in tampons on vaginal cells environment was assessed using a 3D raft culture model. This method utilizes transwells to mimic the vaginal epithelium. In parallel, the influence of pollutants on *Lactobacillus* and dysbtioc species fitness was evaluated using dynamic growth assay. These two technical approaches provide complementary insight into the effect of chemicals on vaginal environment.

Host tissue viability and immune response were evaluated under chemical exposure using transwells method and cytokines quantification. Influence of chemical compounds on *Lactobacillus or Gardnerella* interactions with host cells was also evaluated through their respective modulation of the host immune response. The effect of pollutants on vaginal bacteria species development was separately assessed by monitoring growth rate and fitness over 48 hours of exposure.

This project provides a first insight into the impact of menstrual products on vaginal microbiota and host-bacteria interactions, key components for women's health.

Key words: women's health, vaginal microbiota, host-microbiota interactions, menstrual products

*Intervenant

The Vaginal Microbiota during Pregnancy: Structured Resistomes and Strain-Level Genomics

Sean Kennedy*[1], Nassim Boutouchent*[1,2], and Thi Ngoc Anh Vu[1]

[1]Computational Biology Department, Institut Pasteur, Université Paris Cité – Institut Pasteur de Paris – France

[2]Univ Rouen Normandie, Univ Caen Normandie, INSERM, Normandie Univ, DYNAMICURE UMR 1311, CHU Rouen, Department of Microbiology – Département de Microbiologie [CHU Rouen] – France

Résumé

The vaginal microbiota (VM) is a structured microbial ecosystem that plays a key role in reproductive health and antibiotic resistance dynamics. In a metagenomic analysis of 1,957 samples from pregnant women in the InSPIRe cohort, we identified widespread carriage of acquired antibiotic resistance genes (ARGs), with macrolide and tetracycline resistance genes, including *lsa(C)*, *erm(B)*, and *tet(M)*, among the most prevalent and abundant. These ARGs displayed strong associations with specific microbial community state types (CSTs), and co-abundance networks revealed taxon-specific modularity linking *Gardnerella*, *Prevotella*, and Enterobacterales to distinct ARG and mobile element profiles. The clinical relevance of resistomes are a function of their antibiotics spectrum. To better quantify this functional resistance capacity, we developed the Phenotypic Resistance Diversity Index (PRDI), which we used to reveal a delayed but significant post-antibiotic expansion in resistance breadth. Given this structured resistome landscape, we explored the ecological and genomic basis of dominant CSTs. Focusing on *Lactobacillus crispatus*, *L. iners*, and *Gardnerella vaginalis*, we performed comparative pangenomic (Pan-GWAS) analyses across hundreds of high-quality assembled genomes from our cohort. Substantial species-specific variation in accessory gene content, including mobile elements, adhesion factors, and niche-adaptive traits, was associated with community structure and stability. These findings suggest that strain-level genomic traits shape the structure and resilience of the VM, with implications for ARG carriage, transmission, and new avenues for diagnostics and therapeutic design.

*Intervenant

Pathogen Genomics in Maternal and Neonatal Health: understanding the vaccine targets and mother-to-baby transmission of Group B streptococcus

Elita Jauneikaite*[1]

[1]Institute of Reproduction and Developmental Biology, Imperial College London – Royaume-Uni

Résumé

Streptococcus agalactiae, also known as Group B Streptococcus or GBS, is one of the leading causes of invasive infant infections globally. Approximately 20-30% of healthy adults are carrying GBS asymptomatically in their rectal and vaginal tract. Most commonly, GBS is passed on to the baby during birth and can lead to early onset infections (0-6 days of life) or late-onset infection (7-90days of life). Currently there are no licensed Group B streptococcus (GBS) vaccines, but a hexavalent-polysaccharide (Ia, Ib, II, III, IV, V), and a multivalent-adjuvanted-protein vaccines are in the pipeline. We have investigated the diversity of the GBS population found in mother-baby pairs in the Gambia and have looked at the genetic diversity of vaccine targets in carriage population in the Gambia and disease isolates in the UK.

We have used whole genome sequencing to analyse GBS isolates from carriage samples from mother-baby pairs in the Gambia to determine potential GBS genetic features that can be associated with transmission. As part of the work, we have confirmed that in 65% (15/23) mother-baby pairs had more than one GBS serotype identified, which has potential implications for introduction of GBS vaccines. The genes encoding capsule serotypes in the six-valent GBS vaccine were found in 98-99% of investigated invasive isolates from the UK and the carriage isolates in the Gambia. Proteins, targeted by the protein vaccine were also found in 97-98% of the GBS isolates.

Though the presence of vaccine targeted proteins/serotypes slightly differed between carriage and disease isolates from the Gambia and the UK; nearly all analysed GBS would be covered by the six-valent-polysaccharide GBS vaccine and protein-based GBS vaccine. This data provides evidence for the GBS vaccines phase IV trials as the steps are finalised for the potential inclusion of GBS vaccines into vaccination programme.

*Intervenant

Modeling the vaginal microbiome and its protection against pathogens using the replicator framework for invasion

Tomas Freire*[1], Marina Garcia Romero[2], Sten Madec[3], and Gjini Erida[1]

[1]CEMAT, Instituto Superior Tecnico, University of Lisbon – Portugal
[2]Universitat Politecnica de Catalunya – Espagne
[3]Institut Denis Poisson – Université de Tours – France

Résumé

The human vaginal microbiota play a crucial role in defending against urogenital infections, including bacterial vaginosis, yeast infections, HIV, and urinary tract infections. Yet, the ecological mechanisms that govern this protective function remain poorly understood. In this work, we revisit the pioneering study of Ravel et al. (2010) - which includes vaginal microbiome profiles and Nugent scores for 394 women - and introduce a mechanistic modeling approach based on replicator dynamics to quantify microbial interactions and link community composition to health outcomes. A key challenge lies in the high dimensionality of taxonomic data, which makes ecological models unstable and difficult to interpret. To address this, we reduce the system to 11 dominant microbial species at the phylum level, striking a balance between biological detail and model interpretability. This enables us to fit replicator models with improved stability and estimate interaction parameters using cross-validation across the dataset. While direct prediction of fine-grained Nugent scores remains noisy, grouping scores into three clinically meaningful classes - Healthy, Intermediate, and Unhealthy -substantially improves performance. Our model achieves over 80 % accuracy in classifying vaginal health status from microbiota composition; and benefits further from a biologically motivated nonlinear transformation of Nugent scores into invader growth rates. This framework demonstrates that simple ecological models can capture key links between microbial community structure and clinical health indicators, offering an interpretable and predictive view of vaginal microbiome function.

*Intervenant

Exploring Alternative Metabolism in Lactobacilli for Increased Fitness within the Vaginal Ecosystem

Yusheng Wang*[1], Caroline Dricot[1], Wannes Van Beeck[1], Marc Pons[1], Leonore Vander Donck[1], Tim Van Rillaer[1], Sandra Condori[1], Karolien De Wael[1], and Sarah Lebeer[1]

[1]University of Antwerp – Belgique

Résumé

Vaginal lactobacilli play crucial roles in female health by the inhibition of pathogens and immune modulative effects. In our large-scale citizen science study - Isala, over 70% of women had a lactobacilli-dominated vagina. However, the mechanistic strategies used by lactobacilli to thrive in the vaginal microbial ecosystem remain under investigation. In recent years, extracellular electron transfer (EET) has been reported in lactic acid bacteria (LAB) species, including *Lactiplantibacillus plantarum* and *Lacticaseibacillus rhamnosus*, as a distinct form of energy metabolism. During EET, LAB transport electrons from the cytoplasm to the extracellular environment using shuttles such as 1,4-Dihydroxy-2-naphthoic acid (DHNA) and riboflavin. EET metabolism will lead to redox changes on both sides of the cell membrane, as well as increased metabolic rates and ecological fitness. To date, EET has not yet been studied in vagina-adapted lactobacilli. Our *in-silico* prediction showed that vaginal species including *Lactobacillus crispatus, L. jensenii,* and the genus *Limosilactobacillus* do possess the genetic potential for EET. EET phenotypes of *L. crispatus*, *L. jensenii*, and *Limosilactobacillus* isolated during the Isala project, were validated *in vitro* by ferric reduction assay and electrochemical methods (e.g. chronoamperometry and voltammetry). Strain-specific ferric reductive activities that rely on DHNA were observed in *L. crispatus*, while several promising candidates (2 *L. crispatus*, 2 *L. jensenii*, and 6 *Limosilactobacillus*) were found to generate intense DHNA-dependent current signals in chronoamperometry, confirming the phenotypic potential for EET in vagina-adapted lactobacilli. As the next steps, the effects of EET on growth rate, metabolic activity, and cell viability will be examined, and the influence of EET on vaginal microbiome structure will be explored using synthetic communities. This study will provide new insights into the importance of EET as an alternative metabolism in vaginal lactobacilli, which may contribute to new strategies for the regulation of vaginal microbiome in the future.

*Intervenant

Within-host community dynamics of the vaginal microbiota in young adult women

Quentin Chaung*[1]

[1]Collège de France/ ED 657 SdV – Center for Interdisciplinary Research in Biology (CIRB), College de France, CNRS, INSERM, Université PSL, – France

Résumé

We analyzed data from the PAPCLEAR cohort that followed 189 women aged from 18 to 25 in the area of Montpellier with 974 on-site visits and a total of 1,619 months of follow-up. Building on a first metabarcoding analysis, we performed metagenomics sequencing on a selection of 658 samples from 123 participants.

In our analysis, we leverage this new shotgun metagenomics data to cluster our samples into a finer, new classification of communities with 27 classes known as mgCST (metagenomics CST). We first use this new information to better understand VM stability using a multi-state model.
Second, we investigate the evolution of Lactobacillus crispatus, one of the most frequent species in the human VM. By combining VIRGO2, a gene catalog for VM organisms, and breseq, a software package designed for identifying mutations in longitudinal settings, we look for within-host genetic variation and estimate L. crispatus evolutionary rates.

This represents one of the few studies looking into the evolution of the VM over a long time. A future goal is to get an even finer resolution, going beyond mgCSTs, to understand changes in VM communities over time. Furthermore, for "stable" strains, which remain the dominant species over time in our follow-ups, we will identify substitutions associated to specific effects at cellular and molecular level.
This approach will then be extended to other organisms from the VM, offering a framework to better understand the stability and shifts in vaginal microbiome.

*Intervenant

Uncovering the Evolutionary and Ecological Landscape of Vaginal Prevotella through Genomic Comparisons

Alice Gallot*[1,2], Jacques Ravel[2], Michael France[2], and Melanie Quain[2]

[1]École normale supérieure [ENS] – IBENS, Département de Biologie, École Normale Supérieure, CNRS, INSERM, Université PSL, 75005 Paris, France. – France

[2]Center for Advanced Microbiome Research and Innovation [CAMRI], Institute for Genome Sciences [IGS], University of Maryland Baltimore School of Medicine [UMBSOM], Baltimore MD - USA – États-Unis

Résumé

Bacterial vaginosis (BV) is the most common vaginal infection in women of reproductive age and is linked to increased risks of severe gynecological and obstetric complications. BV is associated with a dysbiosis of the vaginal microbiome and is characterized by a lower abundance of beneficial lactobacilli and a higher abundance of a diverse array of anaerobes, including several species in the genus *Prevotella*. The *Prevotella* species, principally *P. amnii, P. bivia*, and *P. timonensis*, are notable due to their associations with spontaneous preterm birth, and female genital tract infections, including HIV. Despite their importance as a key member of vaginal communities, little is known about the ecology and evolution of these bacteria in the vaginal environment. We compared genomes of several vaginal *Prevotella* species to better describe their functional potential and evolution. Our analysis revealed that several *Prevotella* species (e.g., *P. amnii* and *P. bivia*) have two chromosomes, while others have one (e.g., *P. timonensis*). The multipartite structure of Prevotella genome is a unique opportunity to compare the chromosome architecture of species of the same genus that cohabit in the same ecological niche. Comparative metabolisms reflect Prevotella habitat specificity on the host and their adaptation to the human vagina. Further, the identified metabolic pathways could be leveraged to shift a community away from a dysbiotic state and towards an optimal state dominated by *Lactobacillus spp.* The ecology of Prevotella bacteria can also be seen through its interactions with other bacteria. We characterize the ecological synergetic interaction between co-resident *Gardnerella vaginalis* and Prevotella *spp.* isolates. We examined the genomic capacity of vaginal *Prevotella* species through a lens of ecology and evolution to better understand their function in the vaginal environment and their relationship to vaginal health.

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