



# **Modulation du** microbiote intestinal et l'infectiologie, quoi de neuf ?



Dr KT. GALPERINE

Services Maladies Infectieuses

Centre de transplantation de microbiote intestinal

CHUV. Lausanne

nature  
medicine

CONSENSUS STATEMENT

<https://doi.org/10.1038/s41591-021-01552-x>



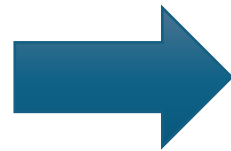
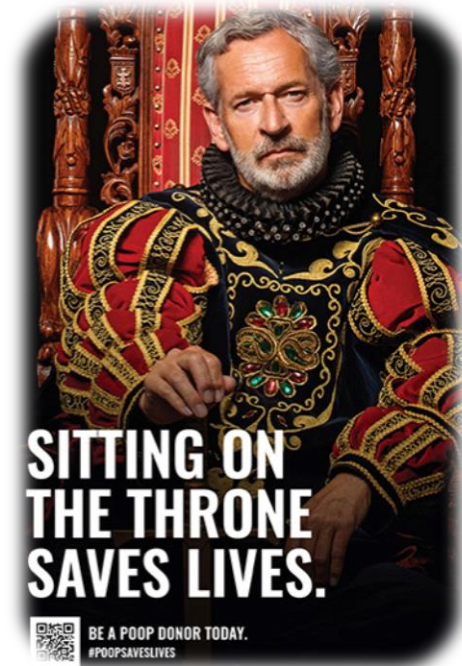
# Reporting guidelines for human microbiome research: the STORMS checklist

# Modulation par les « médicaments » issus du microbiote et Transplantation de microbiote intestinal (fécal) - Infection à *C.difficile*

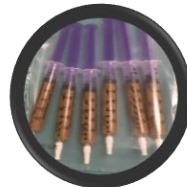


# Pré-requis : Les acteurs des médicaments issus du microbiote

**DONNEUR**



**« MEDICAMENT »**



**PATIENT**



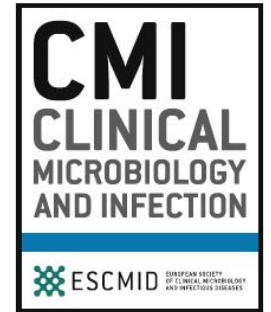


ELSEVIER

Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

## Clinical Microbiology and Infection

journal homepage: [www.clinicalmicrobiologyandinfection.com](http://www.clinicalmicrobiologyandinfection.com)

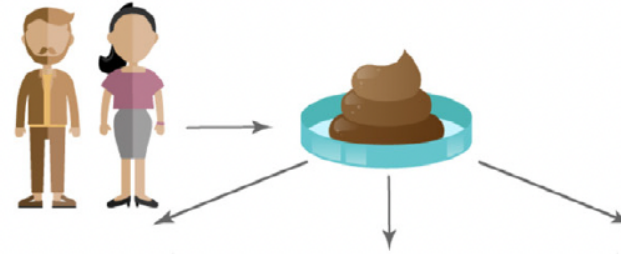




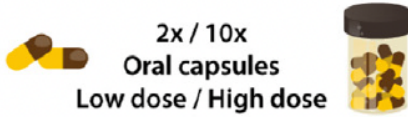
Narrative review

### Update on microbiota-derived therapies for recurrent *Clostridioides difficile* infections, 2023

Nicolas Benech<sup>1, 2, 3, 4, 5, 16, \*</sup>, Frédéric Barbut<sup>1, 5, 6, 7</sup>, Fidelma Fitzpatrick<sup>4, 5, 8</sup>,  
Marcela Krutova<sup>5, 9</sup>, Kerrie Davies<sup>5, 10</sup>, Celine Druart<sup>11</sup>, Magali Cordaillat-Simmons<sup>11</sup>,  
John Heritage<sup>5, 12, 13</sup>, Benoît Guery<sup>4, 5, 14, 16</sup>, Ed Kuijper<sup>4, 5, 15, 16</sup>, on behalf of the ESGCD  
and ESGHAMI<sup>†</sup>

# Médicaments issus du microbiote et Transplantation de microbiote



PRODUCT NAME	RBX2660	SER-109	VE303
PRODUCT TYPE	FMT-DERIVED		BACTERIAL CONSORTIA
STOOL PROCESSING	Dilution (0.9% saline/polyethylene glycol)	Spore enrichment (50 – 70% v/v EtOH 2-hrs treatment)	Bacterial culture (8 strains of Clostridiales)
FORM OF DELIVERY	 Liquid enema	 4x Oral capsules	 2x / 10x Oral capsules Low dose / High dose
REDUCTION OF rCDI	13.1%	28.0%	8.5% / 31.7%
BATCH-TO-BATCH VARIATION	● YES	● YES	● NO
CHARACTERIZATION OF COMPOSITION	● NO	● NO	● YES
RISK OF PATHOGEN (AMR) TRANSMISSION	● POSSIBLE	● POSSIBLE	● LIMITED

**Fig. 1.** Comparison of specificities, safety, and efficacy of microbiota-derived therapies in recurrent *Clostridioides difficile* infection (rCDI). FMT, faecal microbiota transplantation.

# FDA Approves First Fecal Microbiota Product

Product  
Form  
Patients



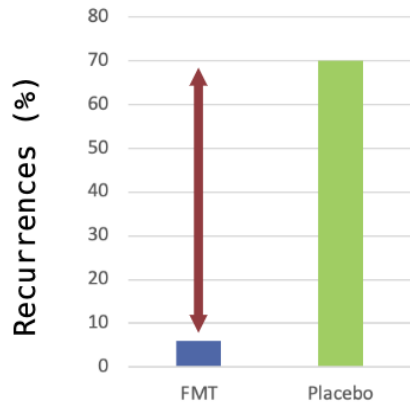
FMT

Fresh, frozen, capsules, enema

Median nb of recc: 3

rCDI Risk Reduction

64%



van Nood et al, N Engl J Med 2013;368:407-15.



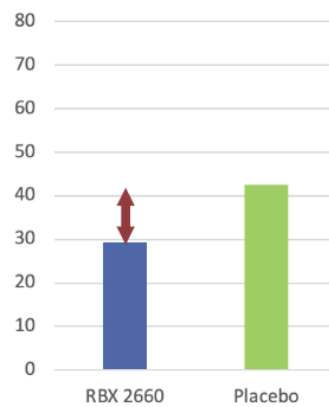
FMT-derived

RBX 2660

Liquid enema

$\geq 1$  recc or  $\geq 2$  severe in the past year

13.1%



Khanna et al, Drugs (2022) 82:1527-1538

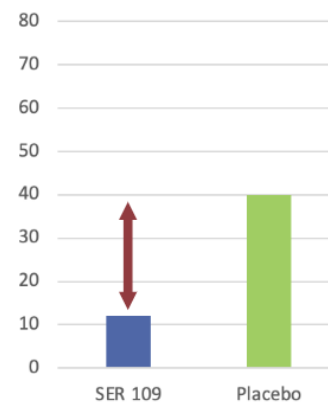


SER 109

Oral capsules

$\geq 3$  CDI within 12 months

28%



Feuerstadt et al, N Engl J Med 2022;386:220-9.



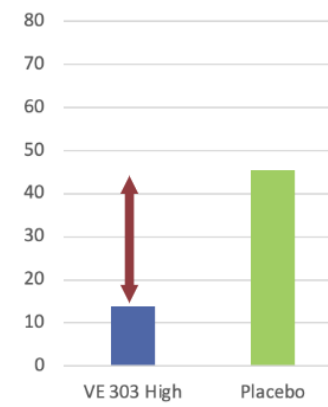
Bacterial consortia

VE 303

Oral capsules

>1 CDI within the 6 months or high risk for recurrence (age + renal insuf, ppi, history of CDI > 6mo)

31.7%



Louie et al, JAMA. 2023;329(16):1356-1366

# Ce qu'il faut retenir sur l'efficacité en 2024...

- **Efficacité de la TMF serait > médicaments pour les infections récidivantes à *C.difficile***
  - Pas d'essai randomisé FMT vs SER 109 ou RBX2660 ou VE303
  - En Europe (?)

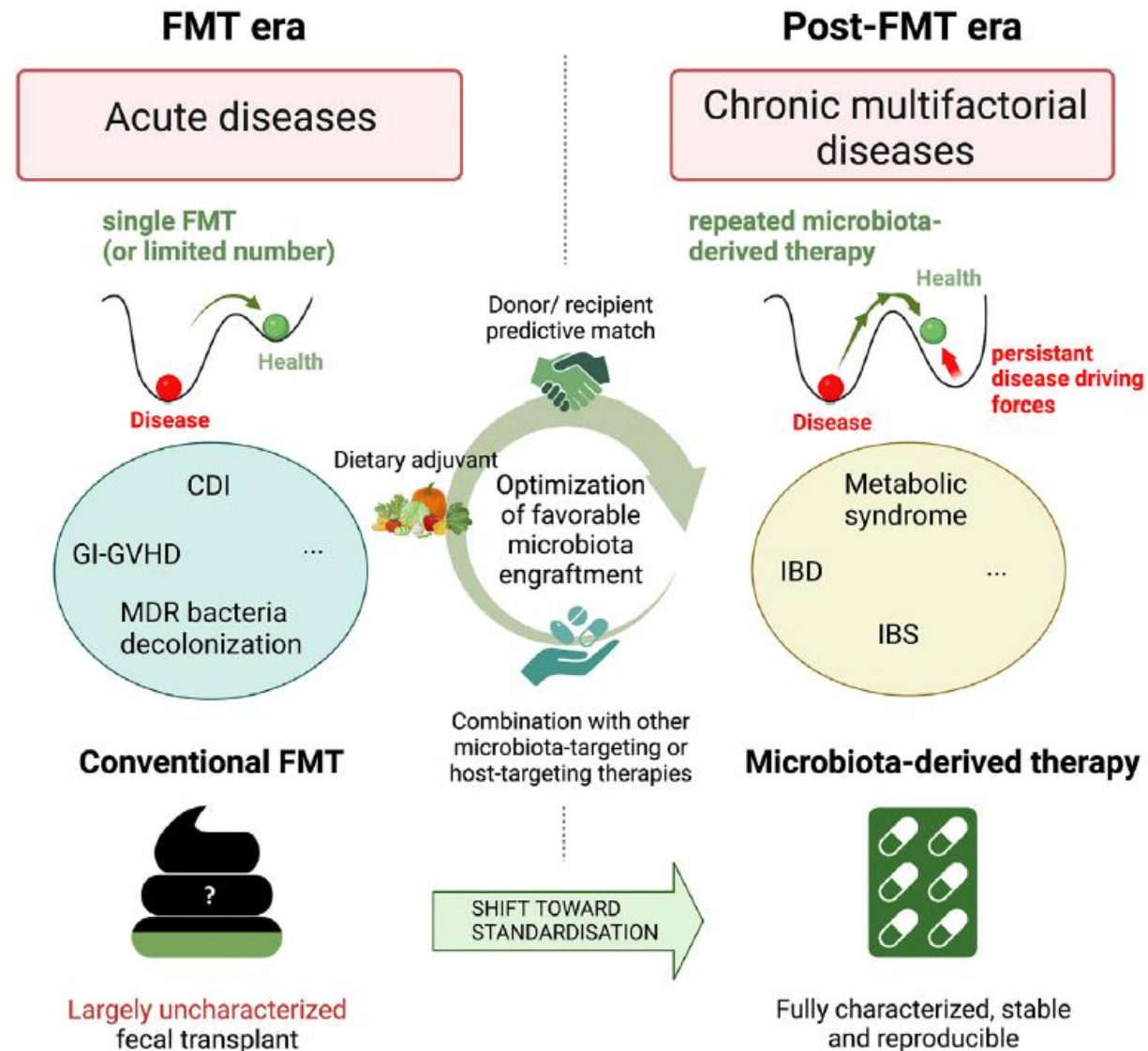
**La TMF dans l'ICD n'est pas dépassée par les médicaments industriels**



- **Sécurité médicaments (24 mois- SER 109) : pas de signal**
  - Quid du **donneur made in USA** (résistome....)
  - Encadrement de l'indemnisation du donneur (30\$ par don RBX2660)
  
- **Sécurité de la TMF (> 10 ans) : pas de signal**
  - Alerte FDA ESBL-shigatoxine : mauvaise pratique de screening
  - Sous déclaration probable
  - Registre en cours ; **France COSMIC** (SPILF-SNFGE)

# Médicaments issus du microbiote vs TMF

Modulation avant  
Chimiothérapie  
Immunothérapie



## GUIDELINES

---

### AGA Clinical Practice Guideline on Fecal Microbiota–Based Therapies for Select Gastrointestinal Diseases



Anne F. Peery,<sup>1,\*</sup> Colleen R. Kelly,<sup>2,\*</sup> Dina Kao,<sup>3,\*</sup> Byron P. Vaughn,<sup>4,\*</sup> Benjamin Lebwohl,<sup>5</sup> Siddharth Singh,<sup>6</sup> Aamer Imdad,<sup>7,§</sup> and Osama Altayar,<sup>8,§</sup> on behalf of the AGA Clinical Guidelines Committee

<sup>1</sup>University of North Carolina, Chapel Hill, North Carolina; <sup>2</sup>Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; <sup>3</sup>University of Alberta, Edmonton, Alberta, Canada; <sup>4</sup>University of Minnesota, Minneapolis, Minnesota; <sup>5</sup>Columbia University, New York, New York; <sup>6</sup>University of California, San Diego, California; <sup>7</sup>University of Iowa, Iowa City, Iowa; and <sup>8</sup>Washington University School of Medicine, St Louis, Missouri

# Nouvelles recommandations USA

TMF ou médicaments industriels = *fecal microbiota–based therapies*

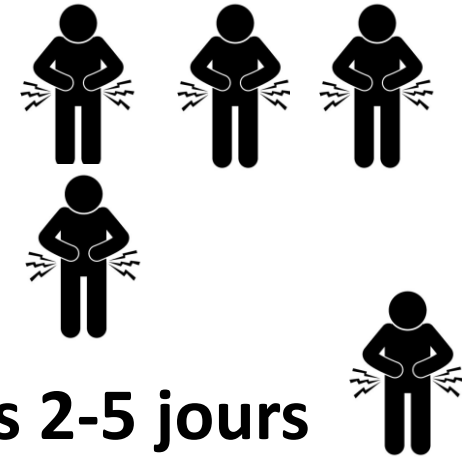
• **Indication : Immunocompétent ou immunosuppression modérée**

- **3 épisodes (2<sup>ème</sup> récurrence)**

- Vancomycine en attente de la TMF
- Traitement anti-ICD terminée

- **Patients à risque de récurrence ou comorbide\***

- **Sévères et Fulminants SI pas de réponses dans les 2-5 jours**



TMF conventionnelle (coloscopie-sigmoidoscopie)

\*ICD sévère, fulminante, comorbidité importante avec conséquences du *C.difficile*

# Nouvelles recommandations USA

- **Indication**

- **PAS chez les patients avec immunodépression sévère\***
  - Rationnel ?
  - *Conditional recommendation, very low certainty evidence*
  - Traitement antibiotique à poursuivre (tapering vancomycine ...)
  - Courrier du GFTF en cours

\*Chimiothérapie active : tumeurs solides - hématologiques, thérapie par cellules CAR T chimeriques ou une greffe de cellules hématopoïétiques (neutropénie), neutropénie, immunodéficience primaire sévère, VIH avancée ou non traitée (CD4 <200/mm<sup>3</sup>)

## La TMF hors infections à *C. difficile* = **RECHERCHE**





Maladie inflammatoire intestinale  
Syndrome du colon irritable


# Ce qu'il faut retenir des recommandations AGA 2024 ...

- 1<sup>ère</sup> recommandation avec des médicaments industriels
- Pas de distinction entre TMF conventionnel et médicament
- TMF : ICD sévères-fulminantes
- Pas de TMF chez immunosupprimé sévère – **NON ACCEPTABLE**
- Pas d'indication en gastro-entérologie hors *C.difficile*

# Recherche sur la galénique pour les ICD



**Maxime Audry**

20 capsules x 2



**Phase I-II in perspective**



**Adèle Rakotonirina**



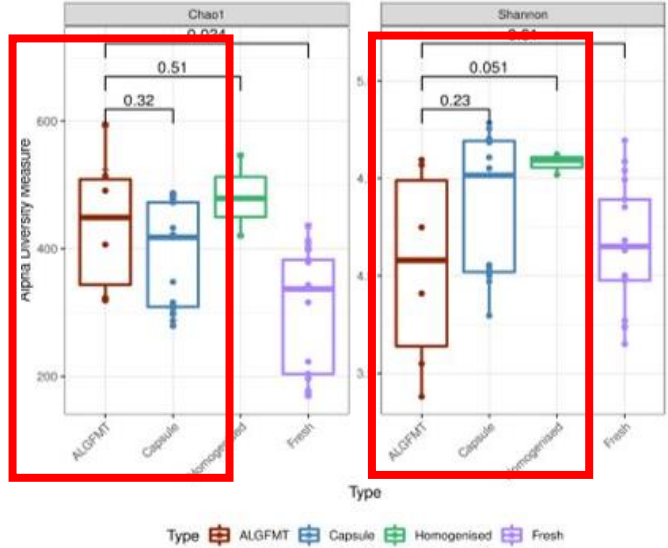
3mm

Freeze-dried

*Rakotonirina A. Expert Opinion on Biological Therapy. 2023;22: 929-944*  
*Rakotonirina A. Int J Pharm. 2023;639:122961*

**Carmen Chen**

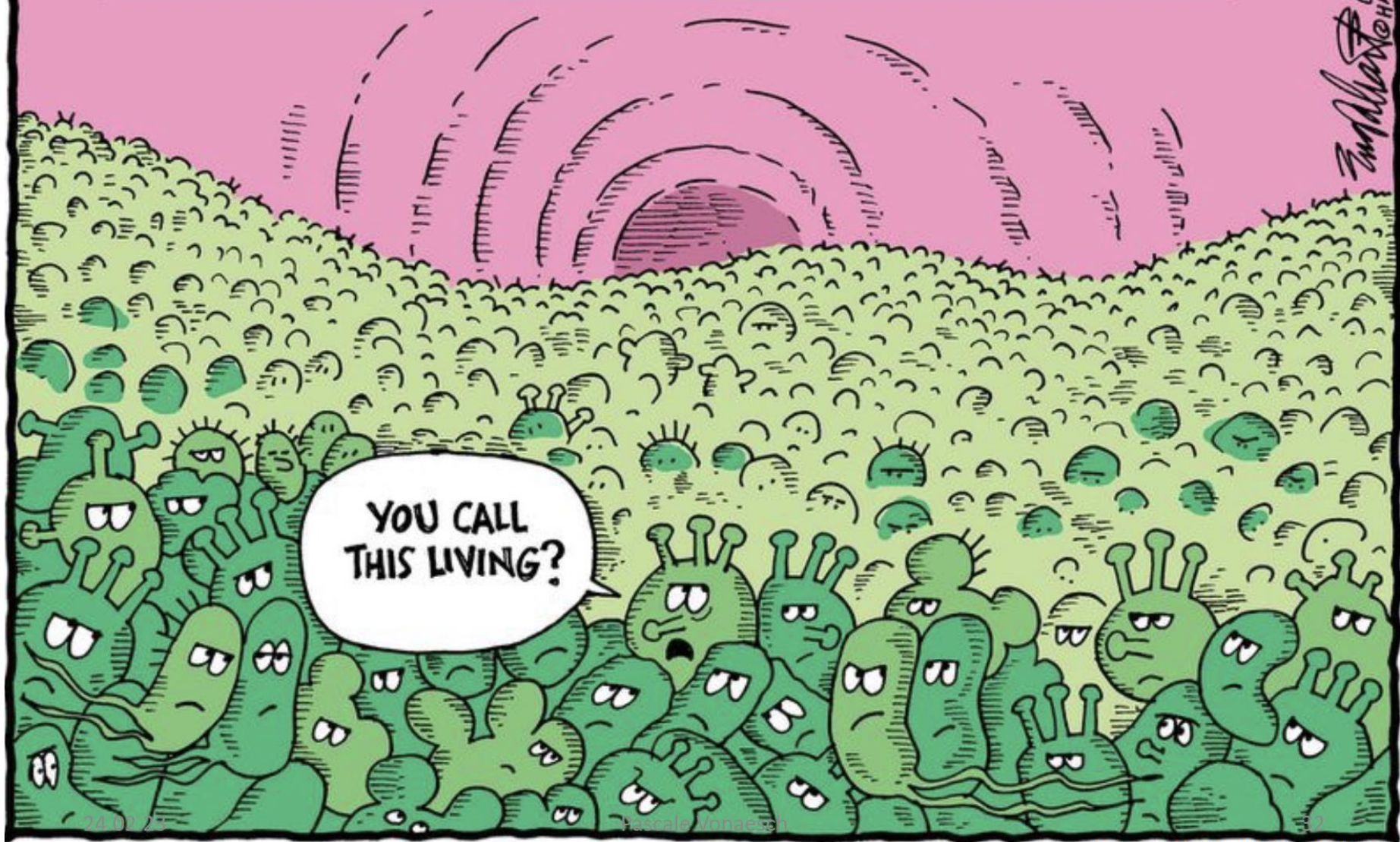


- Comparable bacteria composition between capsules and alginate microbeads

- comparable viability (flow cytometry)

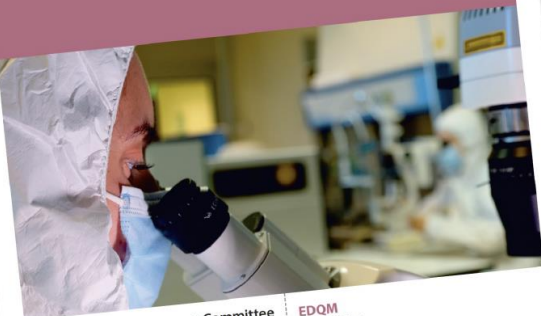


THE HUMAN MICROBIOME PROJECT SAYS THE HUMAN BODY HAS 100 TRILLION MICROSCOPIC LIFE FORMS LIVING IN IT.



6/15/12  
@HARTFORD COURANT

Guide to the quality  
and safety of  
**TISSUES AND CELLS**  
for human application



European Committee  
(Partial Agreement)  
on Organ Transplantation  
(CD-P-TO)

EDQM  
5th Edition  
2022



## Chapter 32: intestinal microbiota

- Legal status
  - Donor recruitment
  - Donor testing
  - Procurement and processing
  - Quality management
  - Labeling and packaging
  - Storage and release
  - Distribution
  - Clinical application
  - Traceability
  - Biovigilance
  - Developing applications
- 
- Monographs
    - Cryopreserved donor faeces capsules
    - Cryopreserved donor faeces suspension



regulation on substances of human origin

## an origin

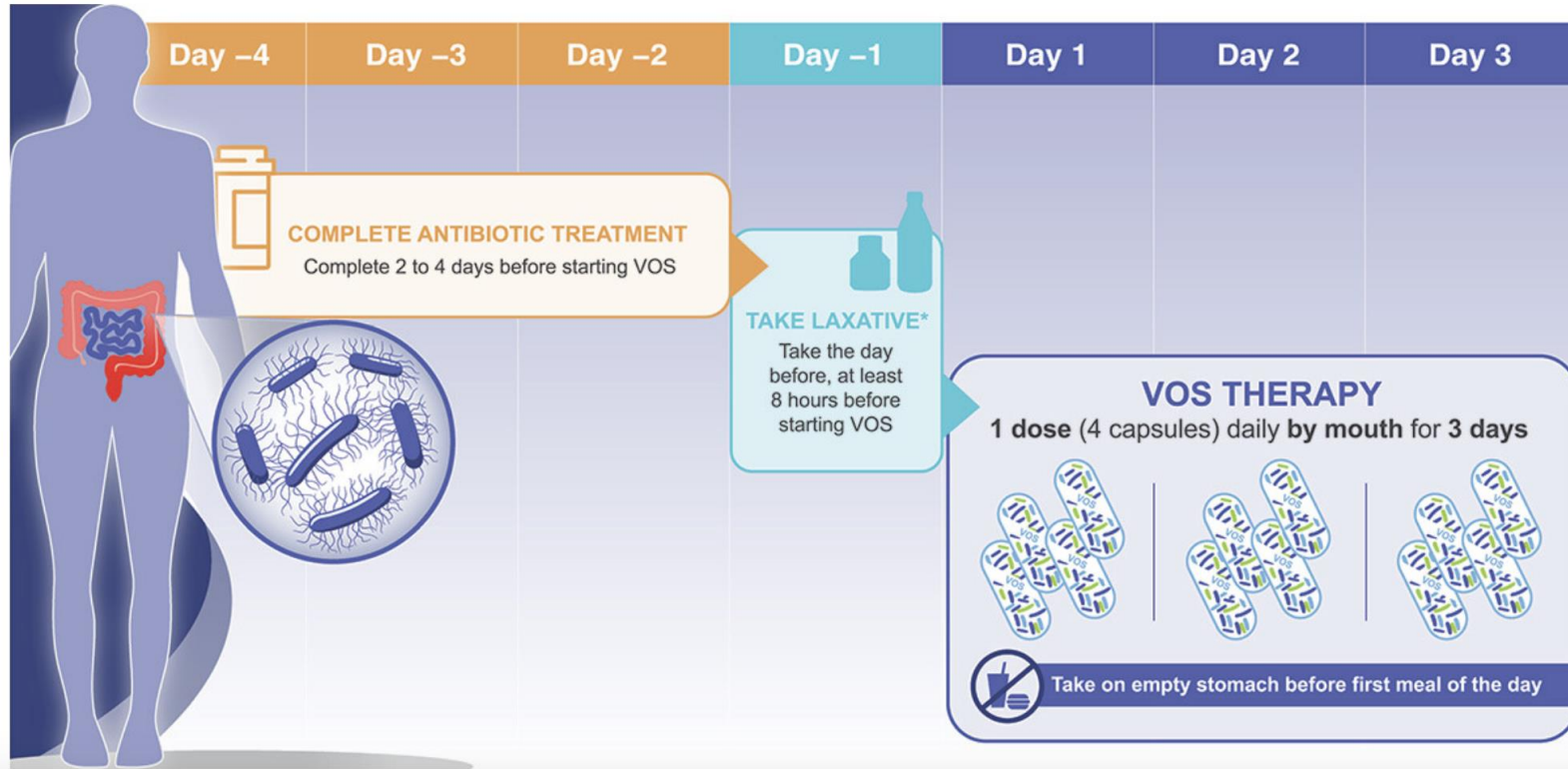
<https://www.edqm.eu/en/>

In July 2022, the European Commission adopted the [proposal for a Regulation](#) { EN | ... } on standards of quality and safety for substances of human origin intended for human application. By repealing the [Blood Directive \(2002/98/EC\)](#) { EN | ... } and the [Tissues and cells Directive \(2004/23/EC\)](#) { EN | ... } (both [evaluated](#) { EN | ... } in 2019), the proposed Regulation concludes the revision of the legal framework for blood, tissues and cells, which was included in the [REFIT Annex \(#37 p.15\)](#) { EN | ... } of the Commission's [Work Programme for 2021](#) { EN | ... }.

PAGE CONTENTS

**Impact assessment**

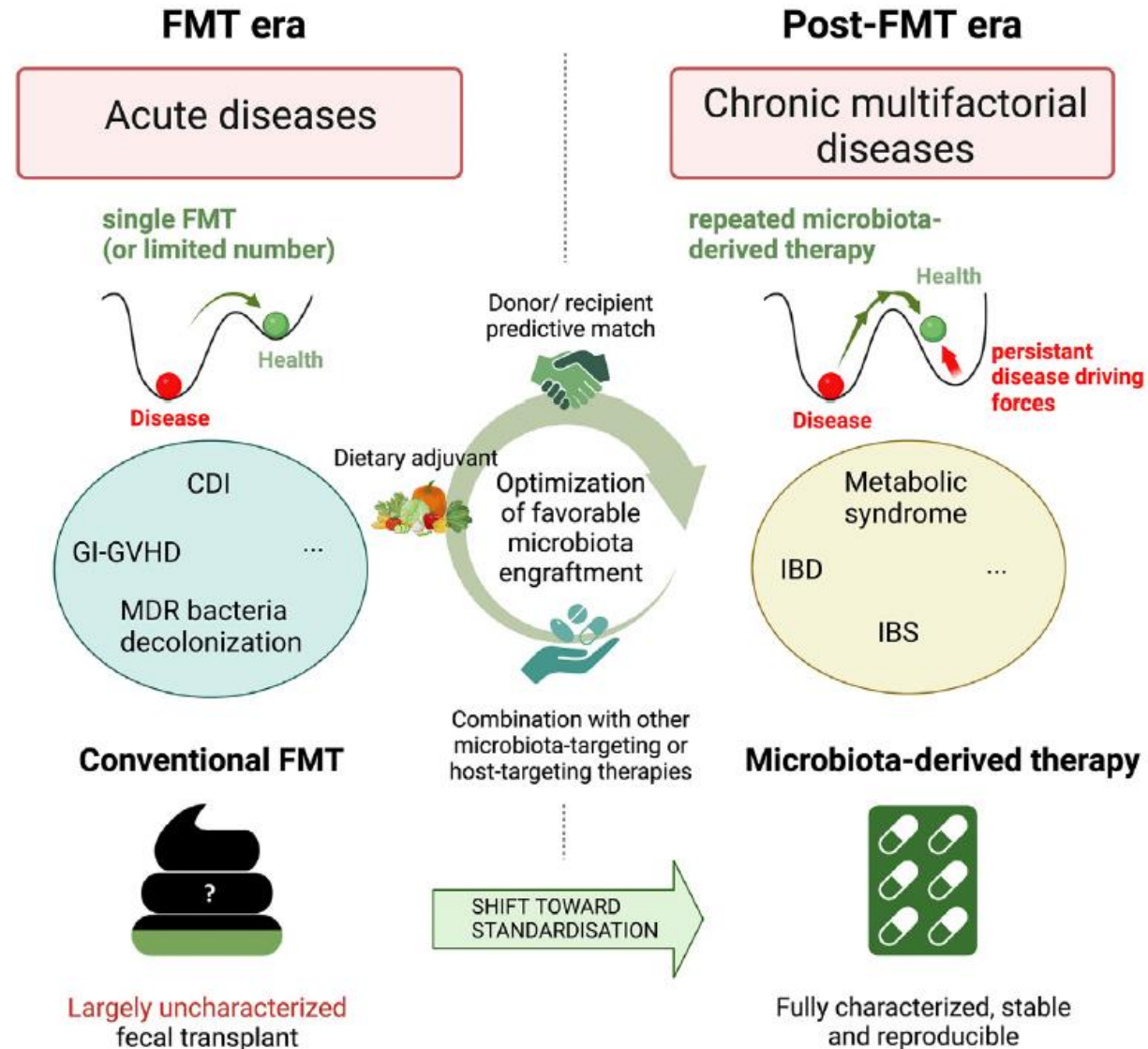
**Next steps**



VOS trials identified patients with CDI in 3 ways: 1) symptomatically with  $\geq 3$  unformed bowel movements over 2 days, 2) objectively with a positive *Clostridioides difficile* toxin test (toxin enzyme immunoassay or cell cytotoxicity neutralization assay) or toxin gene detection via polymerase chain reaction, and 3) in response to antibiotic treatment

# Médicaments issus du microbiote vs TMF

Modulation avant  
Chimiothérapie  
Immunothérapie



### Review

# Key determinants of success in fecal microbiota transplantation: From microbiome to clinic

Serena Porcari,<sup>1,2</sup> Nicolas Benech,<sup>3,4,5,6</sup> Mireia Valles-Colomer,<sup>7</sup> Nicola Segata,<sup>7,8</sup> Antonio Gasbarrini,<sup>1,2</sup> Giovanni Cammarota,<sup>1,2</sup> Harry Sokol,<sup>6,9,10,11</sup> and Gianluca Ianiro<sup>1,2,\*</sup>

<sup>1</sup>Department of Medical and Surgical Sciences, Digestive Disease Center, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

<sup>2</sup>Department of Translational Medicine and Surgery, Università Cattolica del Sacro Cuore, Rome, Italy

<sup>3</sup>Hospices Civils de Lyon, Lyon, France

<sup>4</sup>Université Claude Bernard Lyon 1, Lyon, France

<sup>5</sup>Tumor Escape Resistance and Immunity Department, Cancer Research Center of Lyon (CRCL), Inserm U1052, CNRS UMR 5286, Lyon, France

<sup>6</sup>French Fecal Transplant Group (GFTF), France

<sup>7</sup>Department CIBIO, University of Trento, Trento, Italy

<sup>8</sup>Department of Experimental Oncology, IEO European Institute of Oncology IRCCS, Milan, Italy

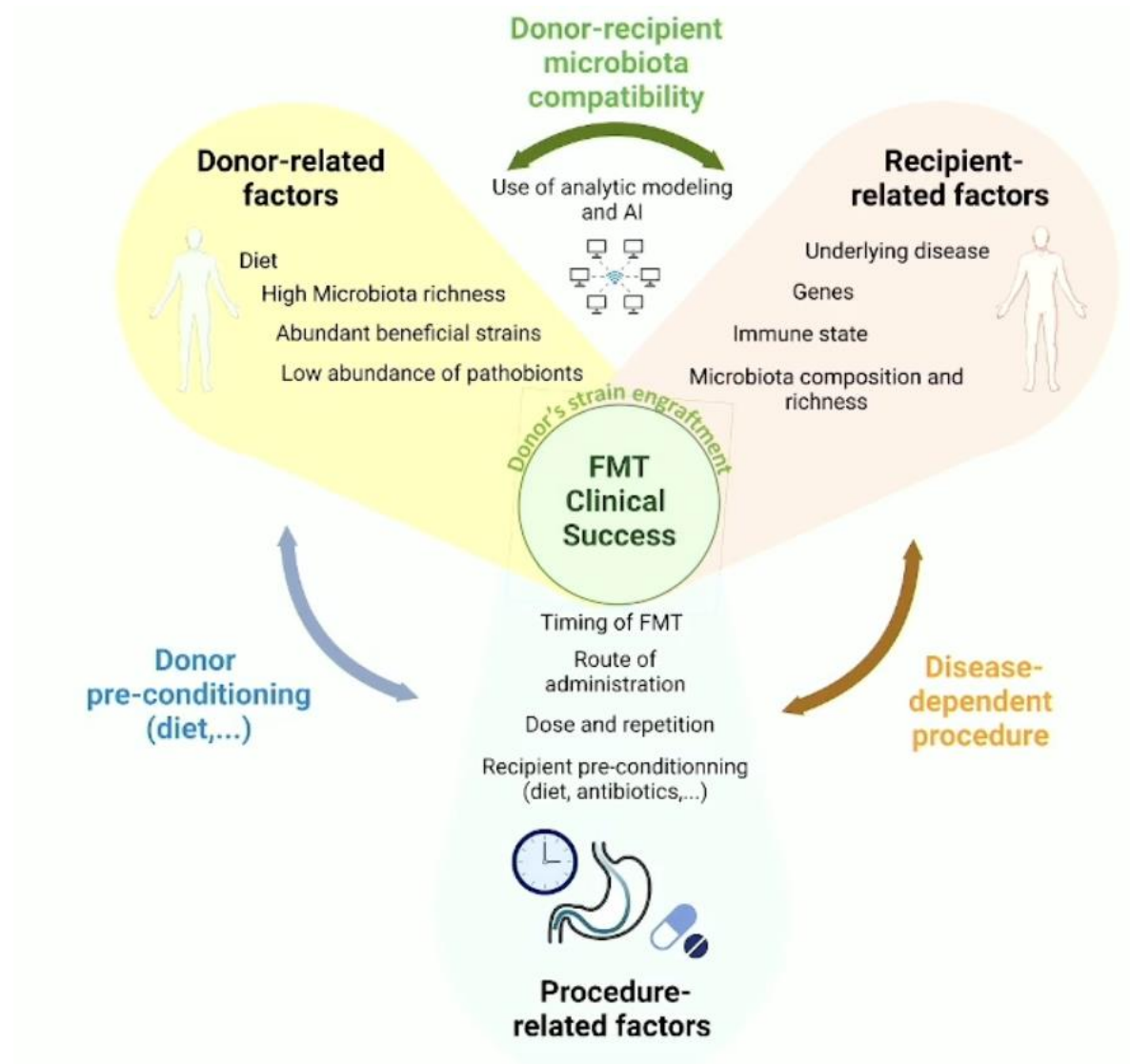
<sup>9</sup>Sorbonne University, INSERM, Centre de Recherche Saint-Antoine, CRSA, AP-HP, Saint Antoine Hospital, Gastroenterology Department, Paris, France

<sup>10</sup>Paris Centre for Microbiome Medicine FHU, Paris, France

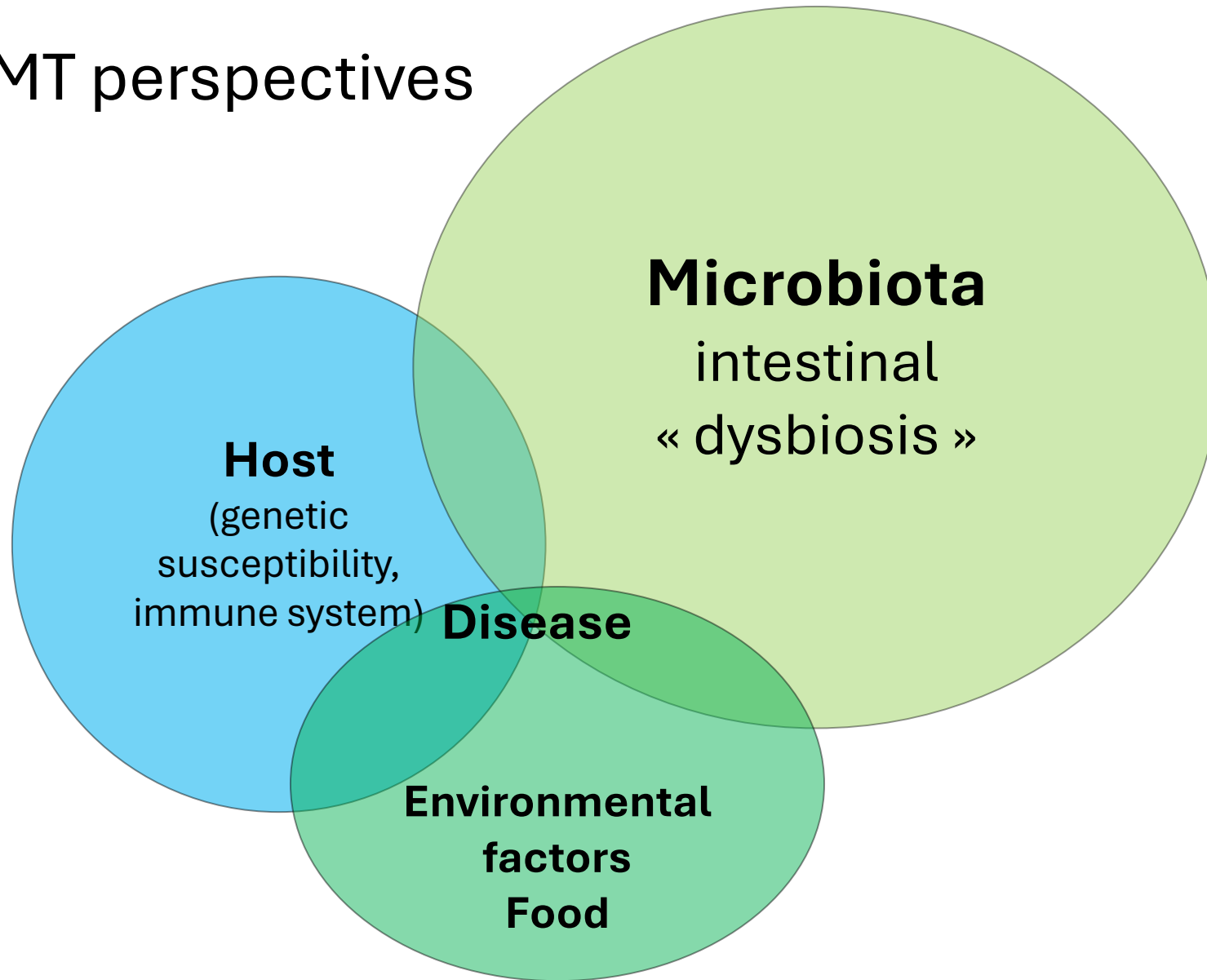
<sup>11</sup>INRA, UMR1319 Micalis & AgroParisTech, Jouy en Josas, France

\*Correspondence: [gianluca.ianiro@unicatt.it](mailto:gianluca.ianiro@unicatt.it)

<https://doi.org/10.1016/j.chom.2023.03.020>



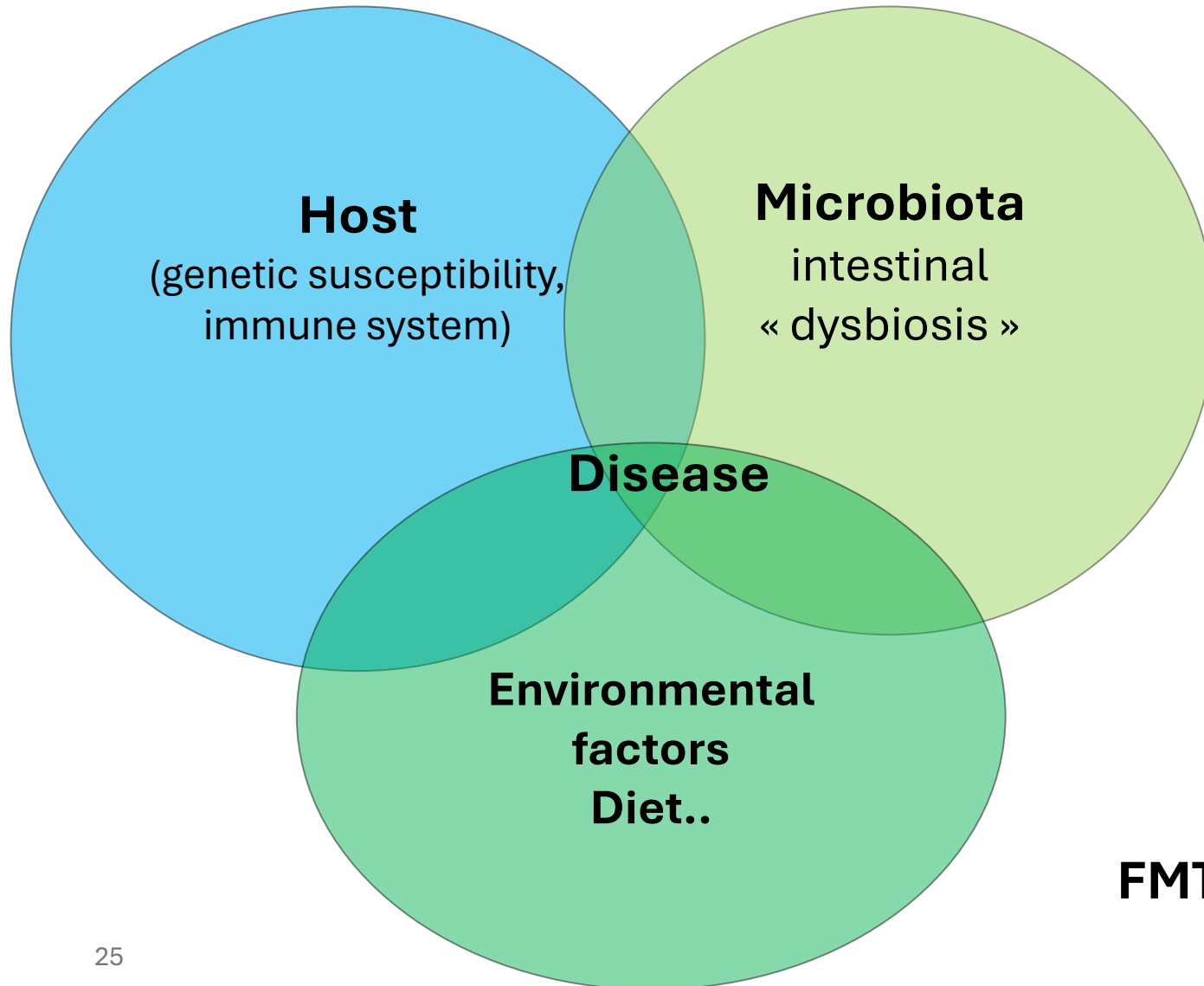
# FMT perspectives



**CDI** : earlier administration (first episode or first recurrence)

**Restoration of the gut microbiota** after large spectrum antibiotic in targeted population (immunosuppressed (solid organ transplant), or in the intensive care)

# FMT perspective in other indications



## **Only for acute disease**

Modulation of the gut microbiota  
In cancer, immunotherapy  
(efficacy, tolerance and side effect)

Research: Identify the optimal characteristics of FMT donors, recipients and FMT procedures (route of administration, antibiotic pretreatment, bowel preparation, repeated FMT..)

**FMT could be an adjuvant treatment?**