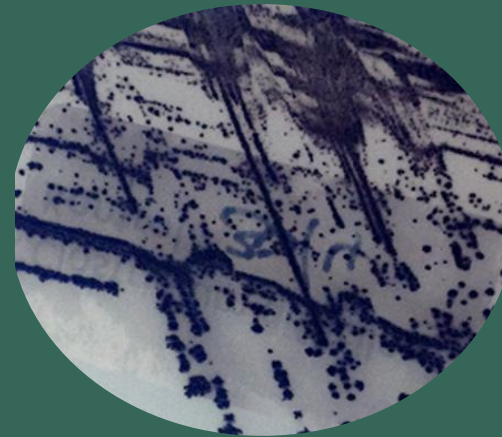


Infections récurrentes à *Clostridioïdes difficile*

JOURNÉE DES RÉFÉRENTS EN ANTIBIOTHÉRAPIE

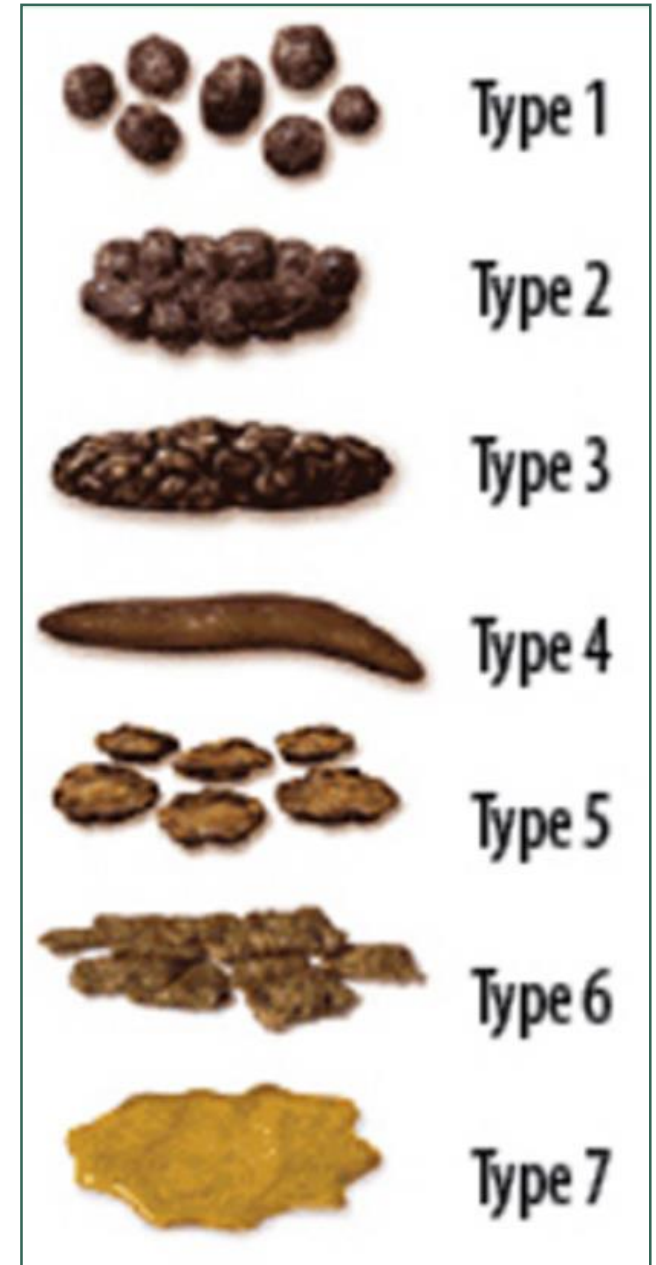
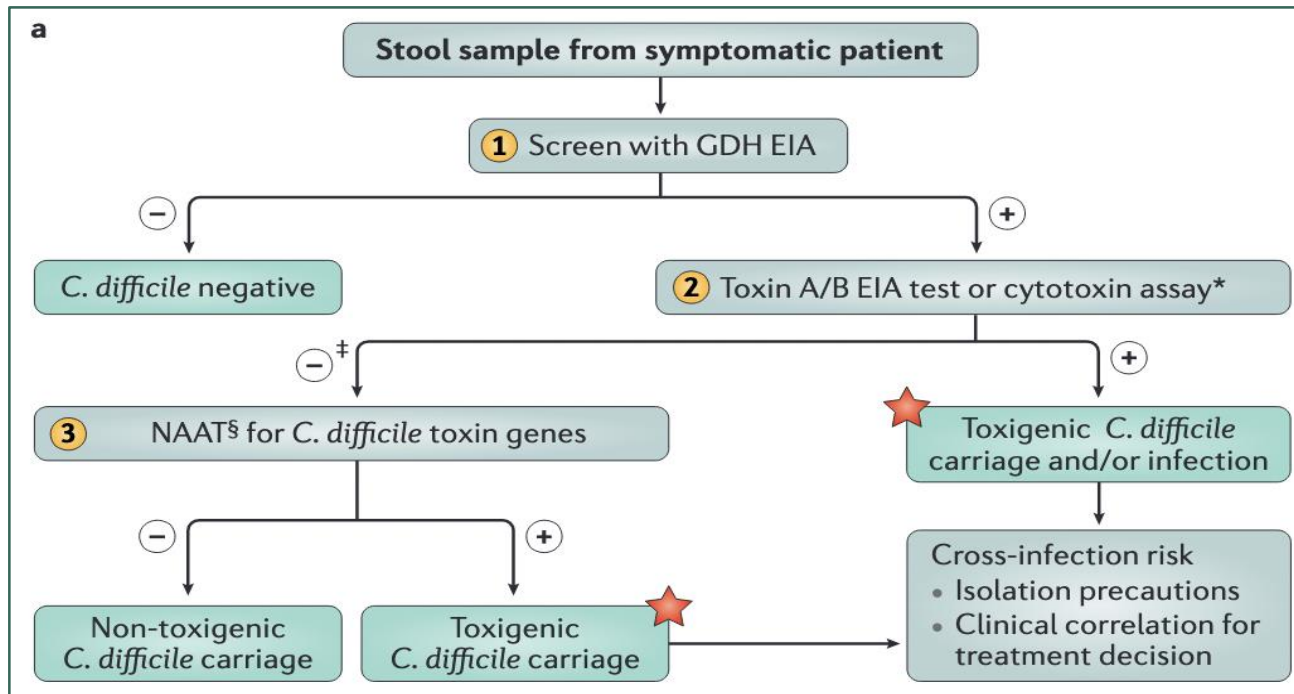
04/02/2025



Sarah STABLER
Unité de maladies infectieuses – CHU Lille

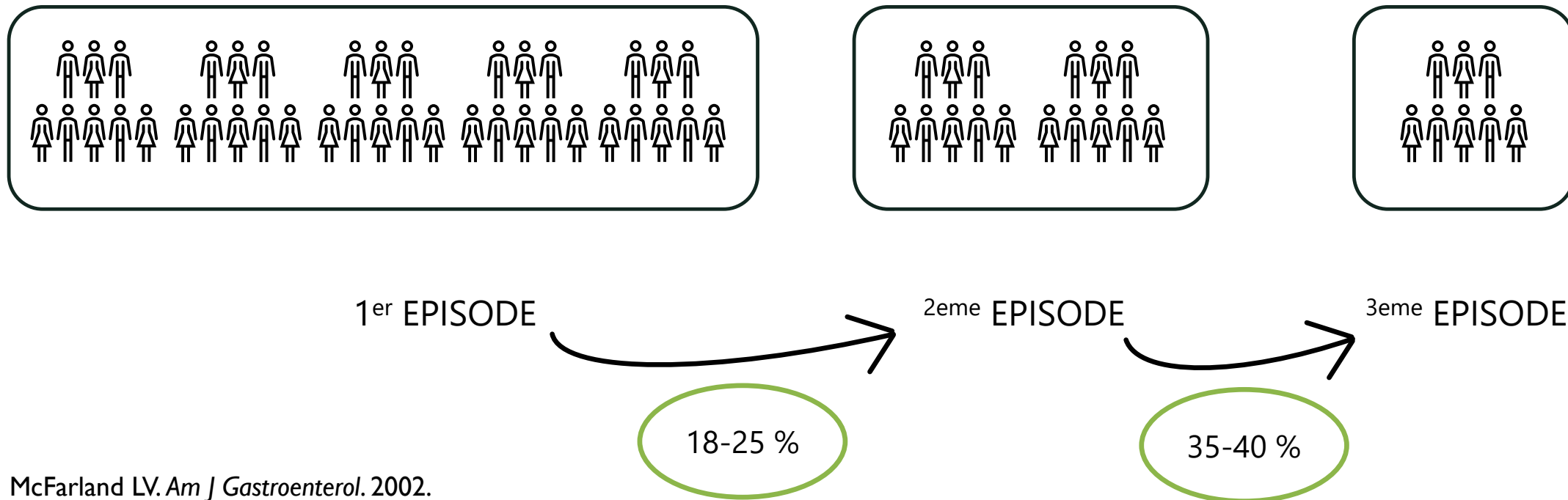
Colite à *Clostridioïdes difficile*

I - Diarrhée: au moins 3 selles/jr de type Bristol 5 à 7 > 48H
OU iléus
OU mégacôlon toxique
(diamètre du colon transverse > 6 cm)

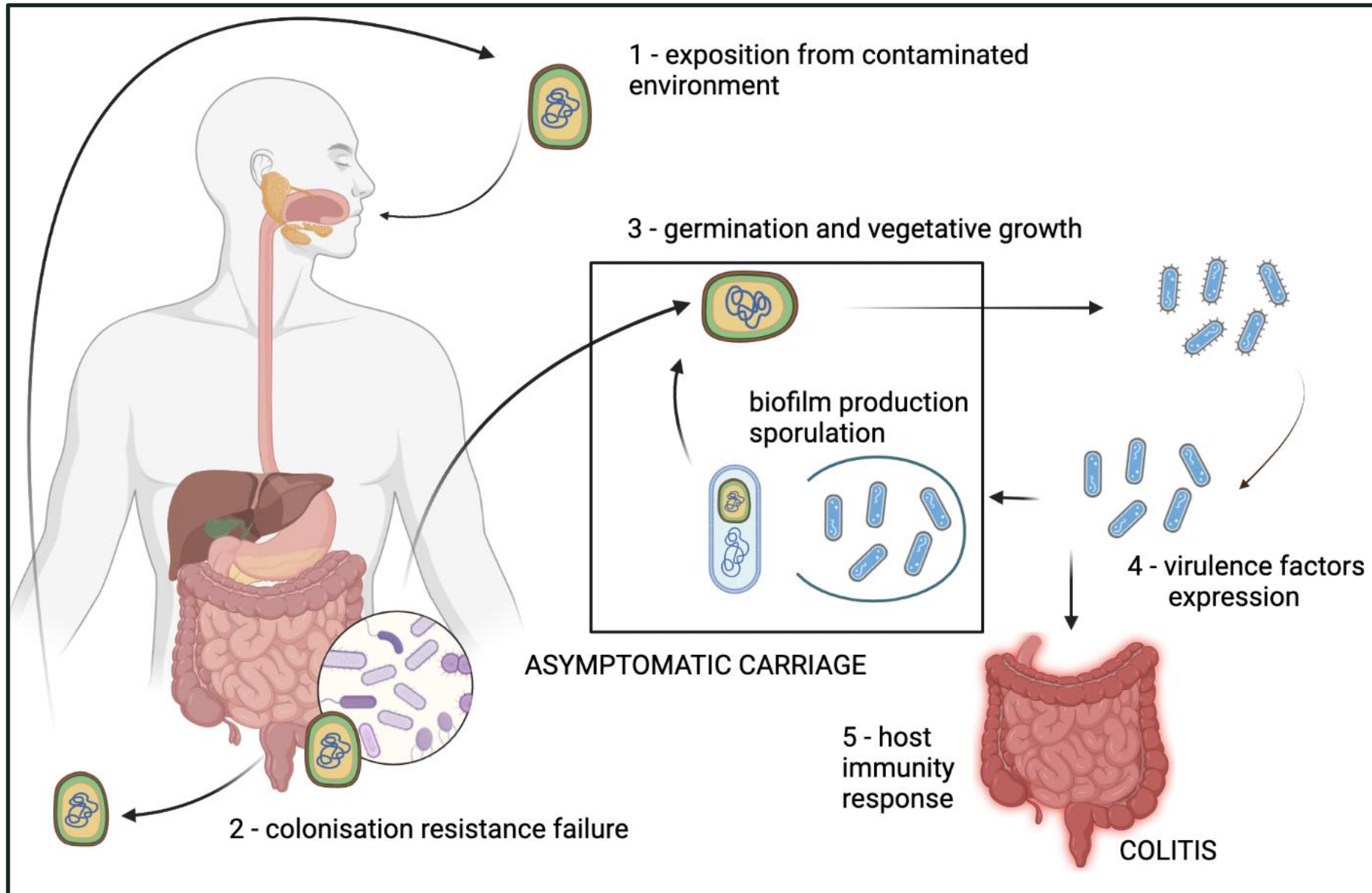


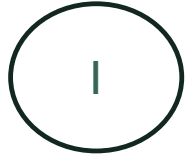
Problématique des infections à *Clostridioïdes difficile* = RECURRENCES

= Récidive des diarrhées dans les 8 semaines suivant le traitement d'une ICD
+ Recherche de *Clostridium* toxinogène positive
+ **Absence de diagnostic différentiel**



1. McFarland LV. *Am J Gastroenterol*. 2002.
2. Lessa FC, *NEJM* 2015.
3. Huang AM, *Transpl Infect Dis*. 2014
4. Sheitoyan-Pesant, *CID* 2016






1 Identifier les patients qui vont récidiver

Table 1. Risk Factors for Recurrent *Clostridium difficile* Infection

Advanced age
Antibiotics use for non-*C. difficile* after CDI diagnosis
Gastric acid suppression
Hypervirulent strain, NAP1/BI/027
Severe underlying disease and/or renal insufficiency
History of previous CDI
Previous CDI severity
Prolonged hospital stays
Lack of adaptive immune responses to toxins A and B

CDI, *C. difficile* infection.



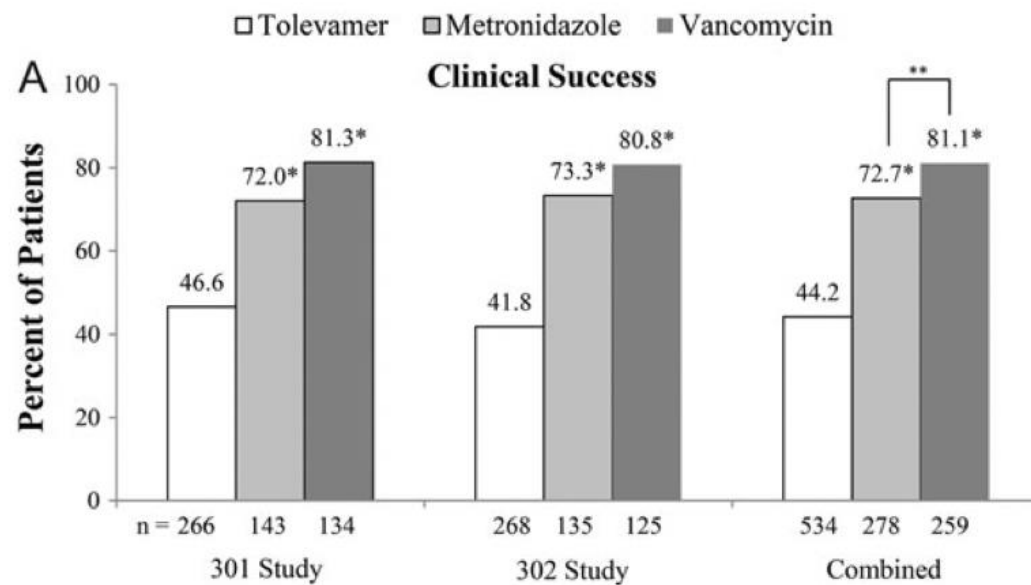
1

Identifier les patients qui vont récidiver

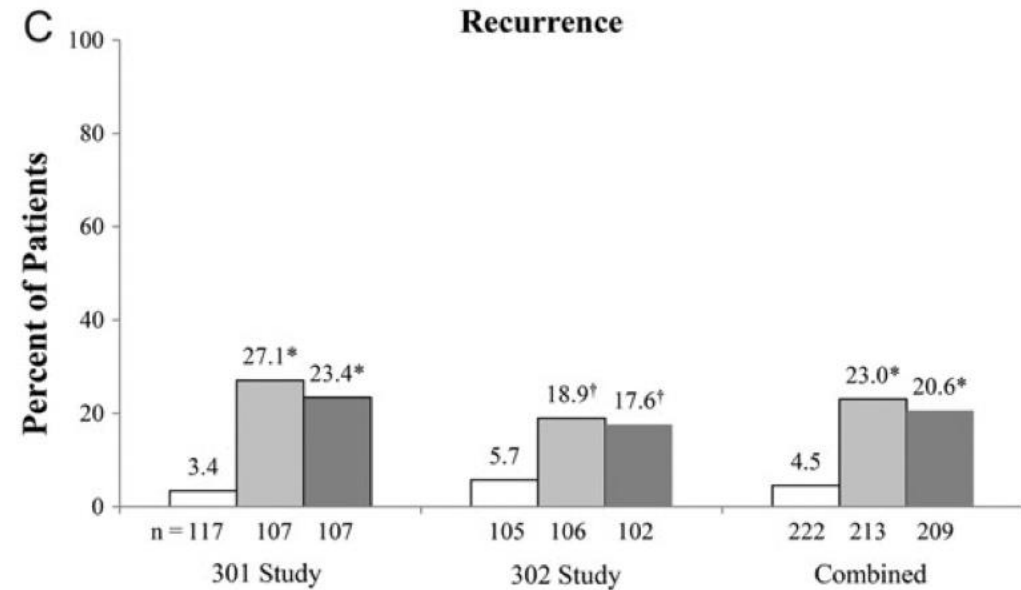
2

Comment optimiser le traitement de première ligne ?

Le Métronidazole FLAGYL : c'est FINI !

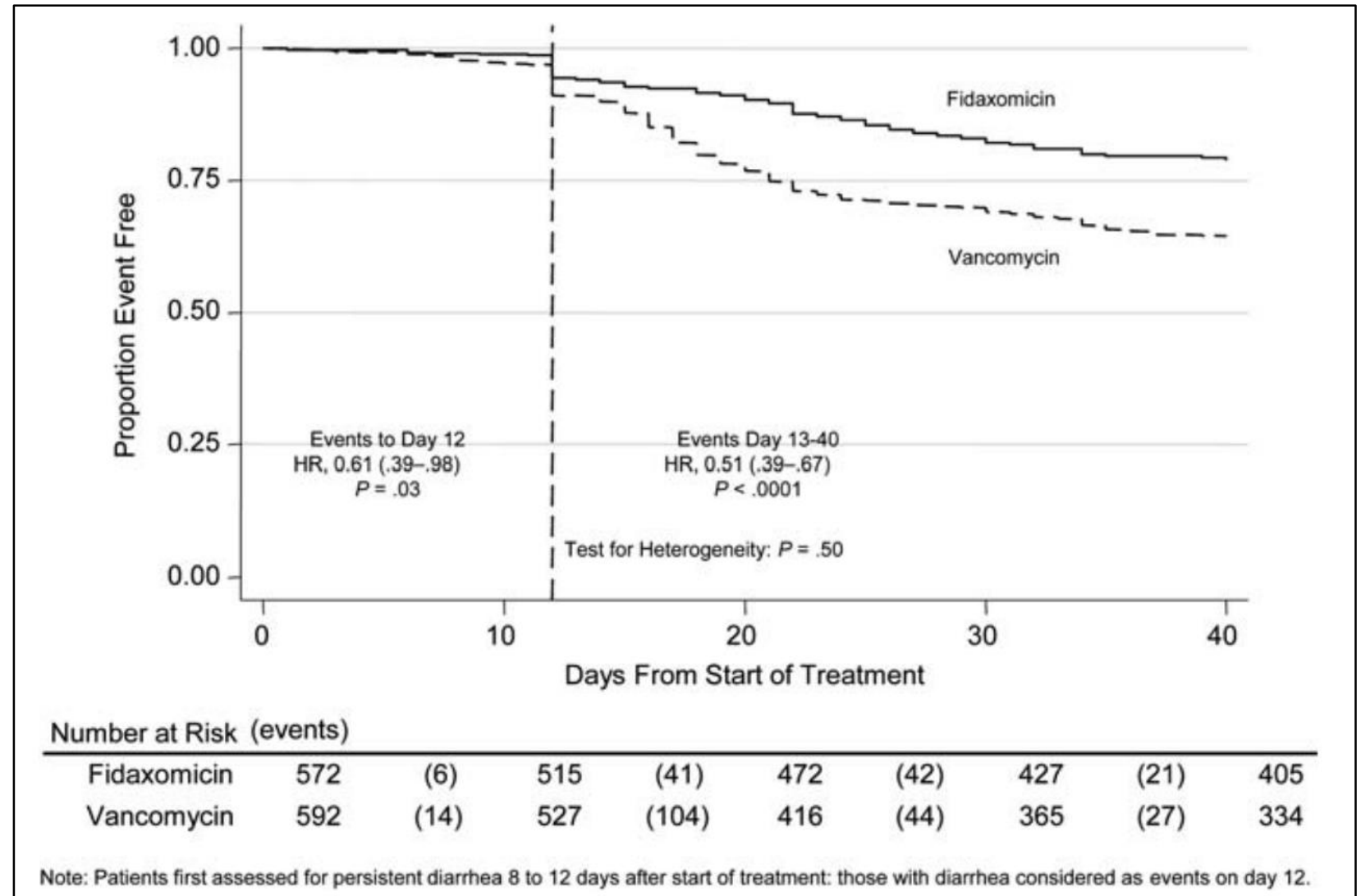


MOINS DE GUERISON



PLUS DE RECHUTE

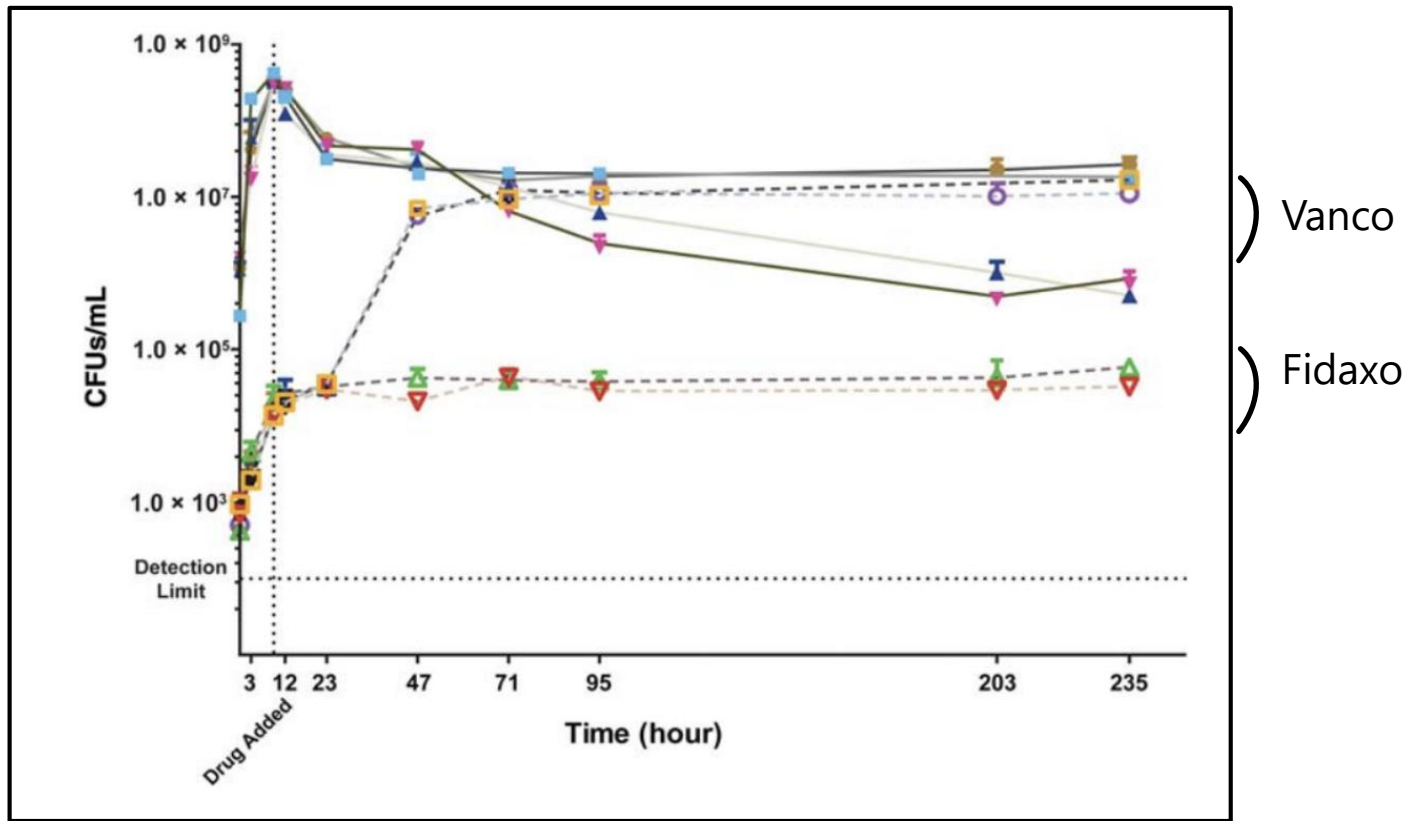
Fidaxomicine DIFICLIR à l'honneur



Crook, Clin Inf Dis, 2012
 Cornely OA, Lancet Infect Dis, 2012.
 Louie TJ, N Engl J Med 2011.

Fidaxomicine DIFICLIR à l'honneur

INHIBITION DE LA SPORULATION

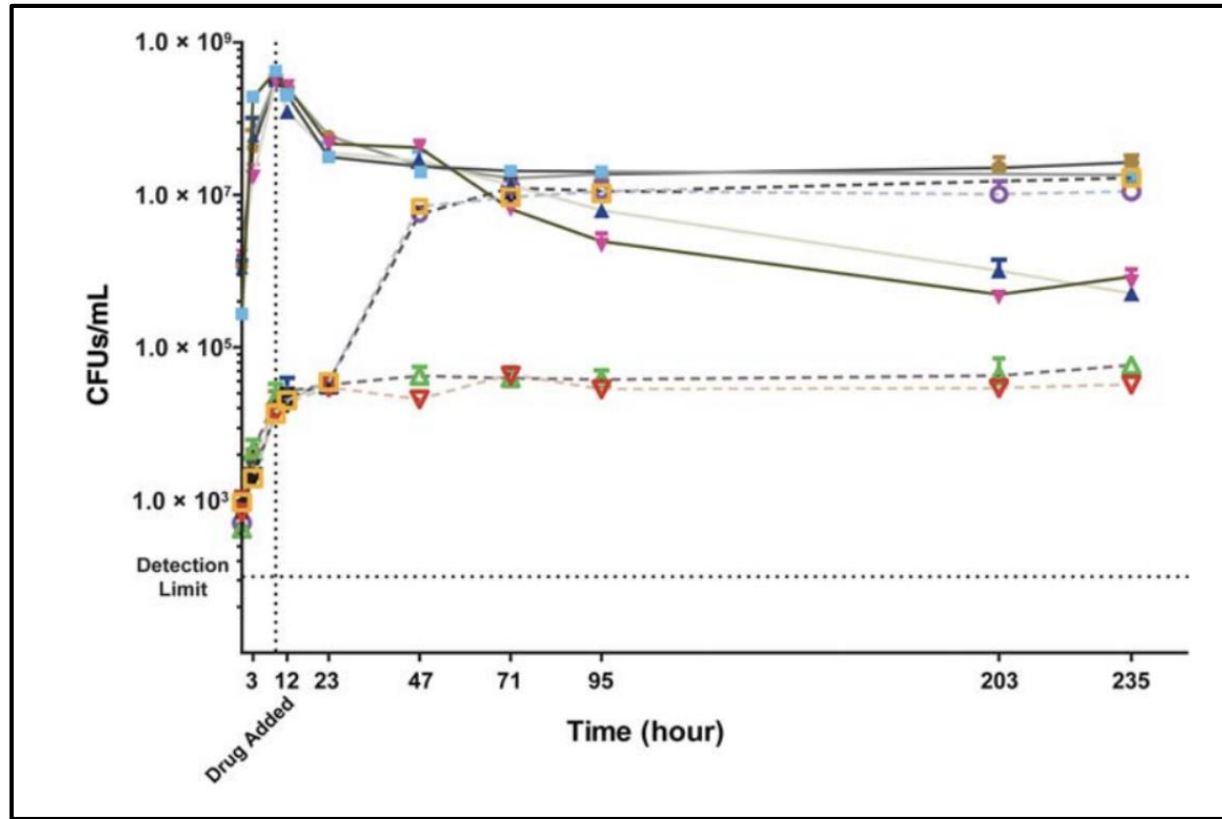


Babakhani, CID, 2012
Louie, CID, 2012

absence of drugs (●, ○),
fidaxomicin (FDX) (▲, △),
vancomycin (■, □)

Fidaxomicine DIFICLIR à l'honneur

INHIBITION DE LA SPORULATION



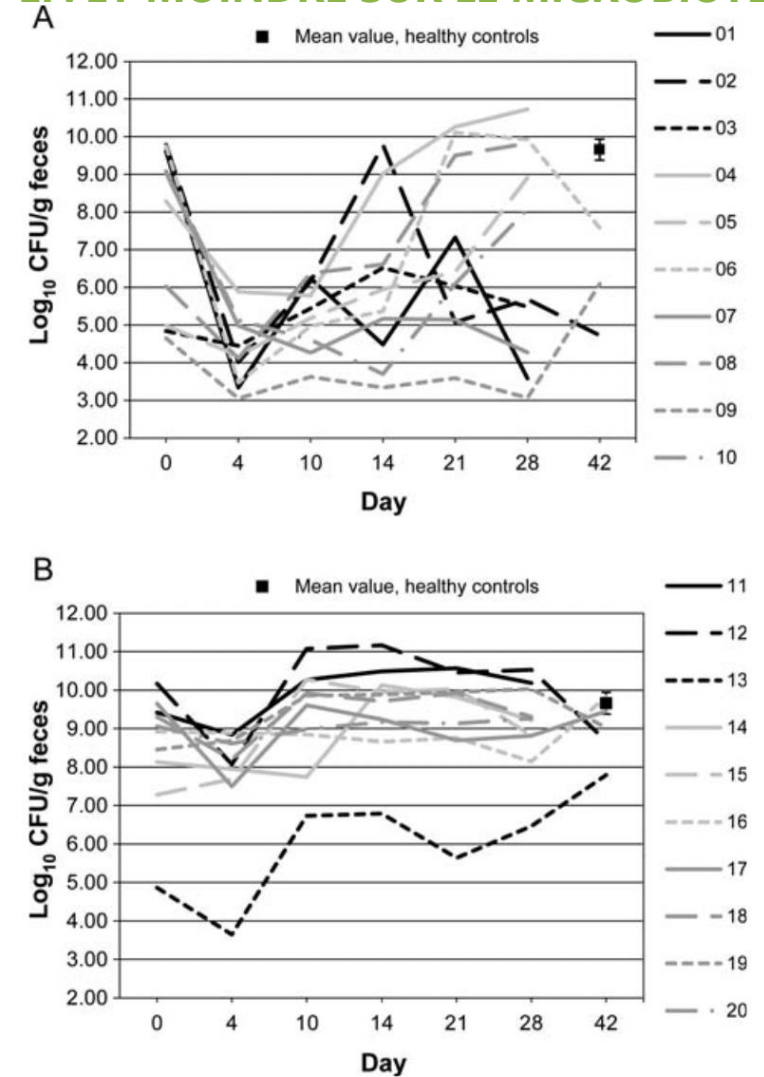
Vanco

Fidaxo

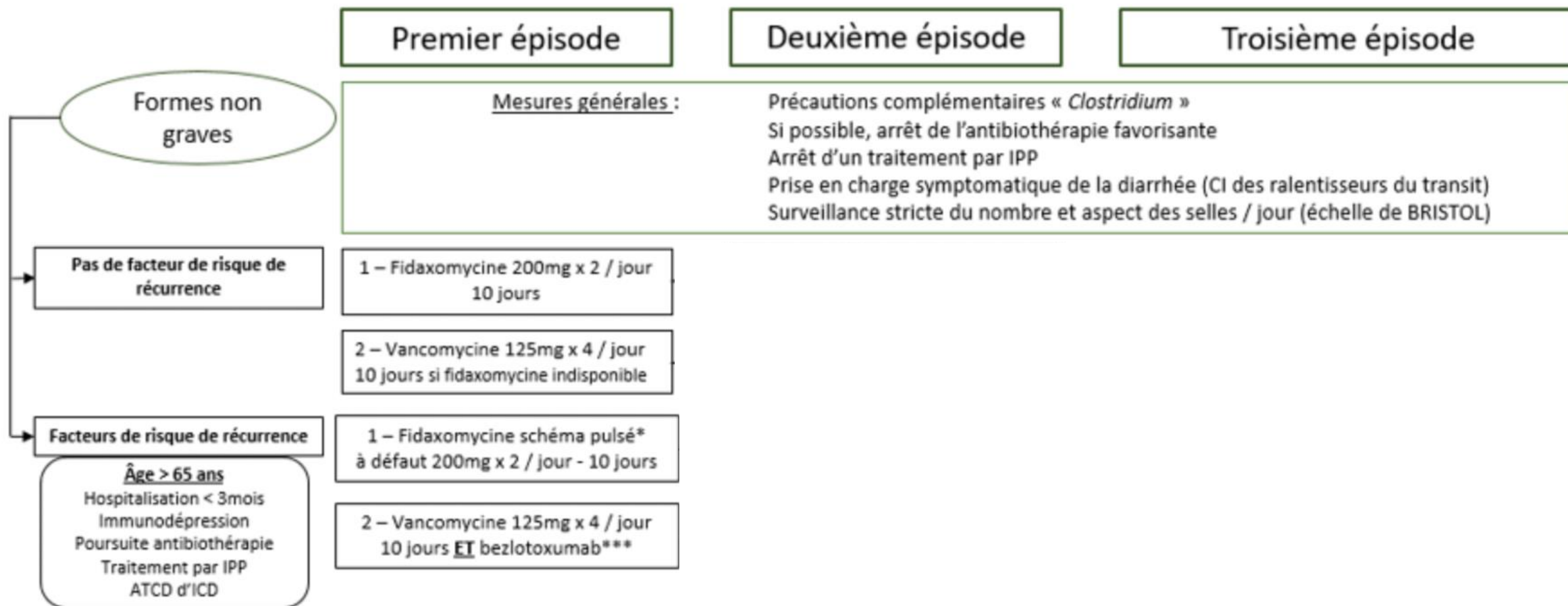
Babakhani, CID, 2012
Louie, CID, 2012

absence of drugs (●, ○)
fidaxomicin (FDX) (▲, △)
vancomycin (■, □)


EFFET MOINDRE SUR LE MICROBIOTE




Protocole du CHU Lille - 2022



Docteur Jean-Paul Santé
Médecine Générale
Maison Médicale
39 Avenue Jules Verne
75001 Paris
Tél : 09 99 99 99 99
Consultation sur rendez-vous
tous les jours sauf le jeudi après-midi


N°AM

141006XXX

Vancomycine 125mg * 4 / jour
10 jours


N°RPPS

1002420XXX

En cas d'urgence en mon absence, composez le 15.
En l'absence d'une association de gestion agréée, le règlement des honoraires par chèque est accepté.

Docteur Jean-Paul Santé
Médecine Générale
Maison Médicale
39 Avenue Jules Verne
75001 Paris
Tél : 09 99 99 99 99
Consultation sur rendez-vous
tous les jours sauf le jeudi après-midi

N°AM

141006XXX

Fidaxomicine 200mg * 2 / jour
10 jours

N°RPPS

1002420XXX

En cas d'urgence en mon absence, composez le 15.
En l'absence d'une association de gestion agréée, le règlement des honoraires par chèque est accepté.

Organisation de la filière de téléexpertise



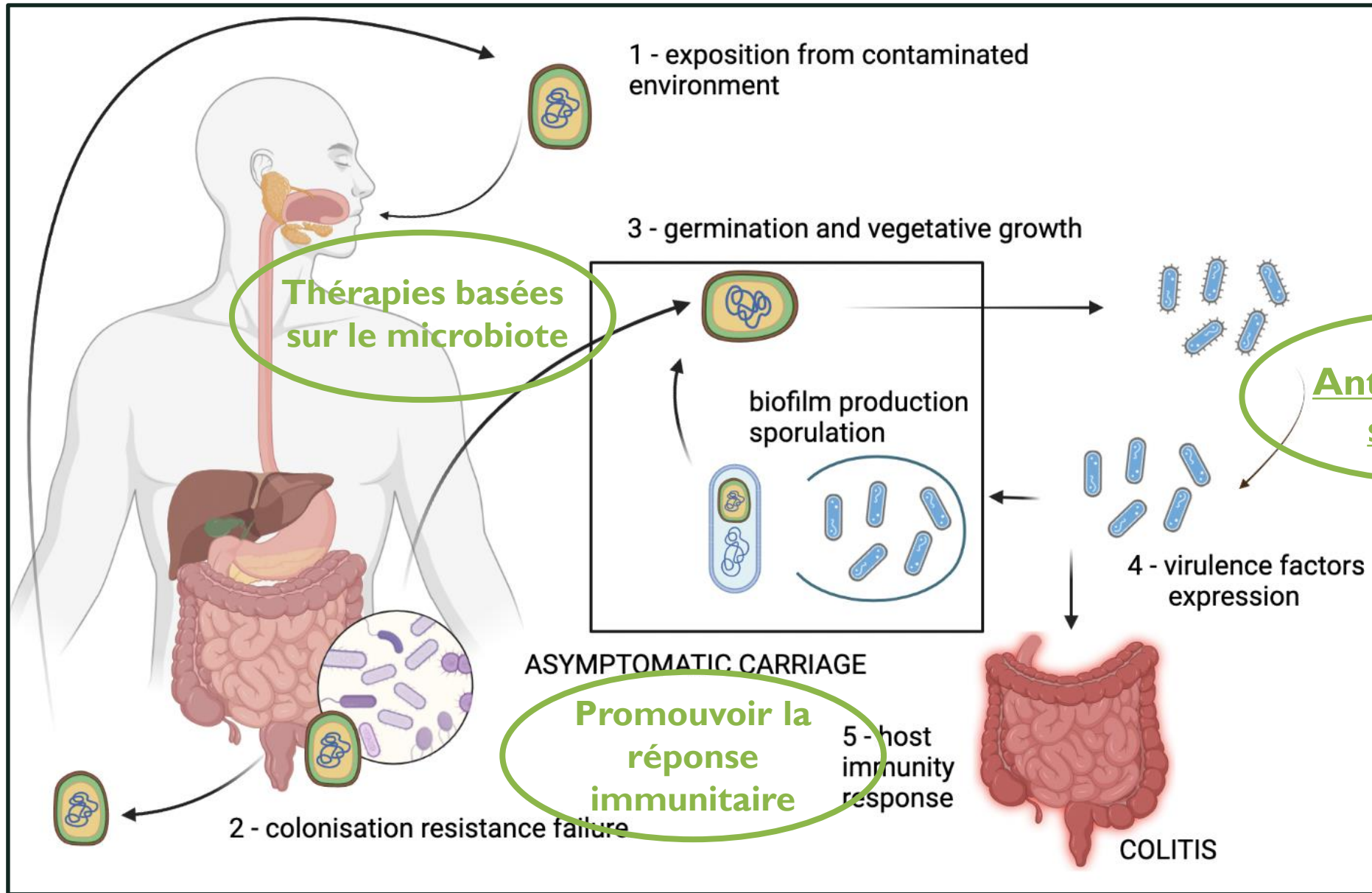
RETROCESSION HOSPITALIERE
PRESCRIPTION HOSPITALIERE



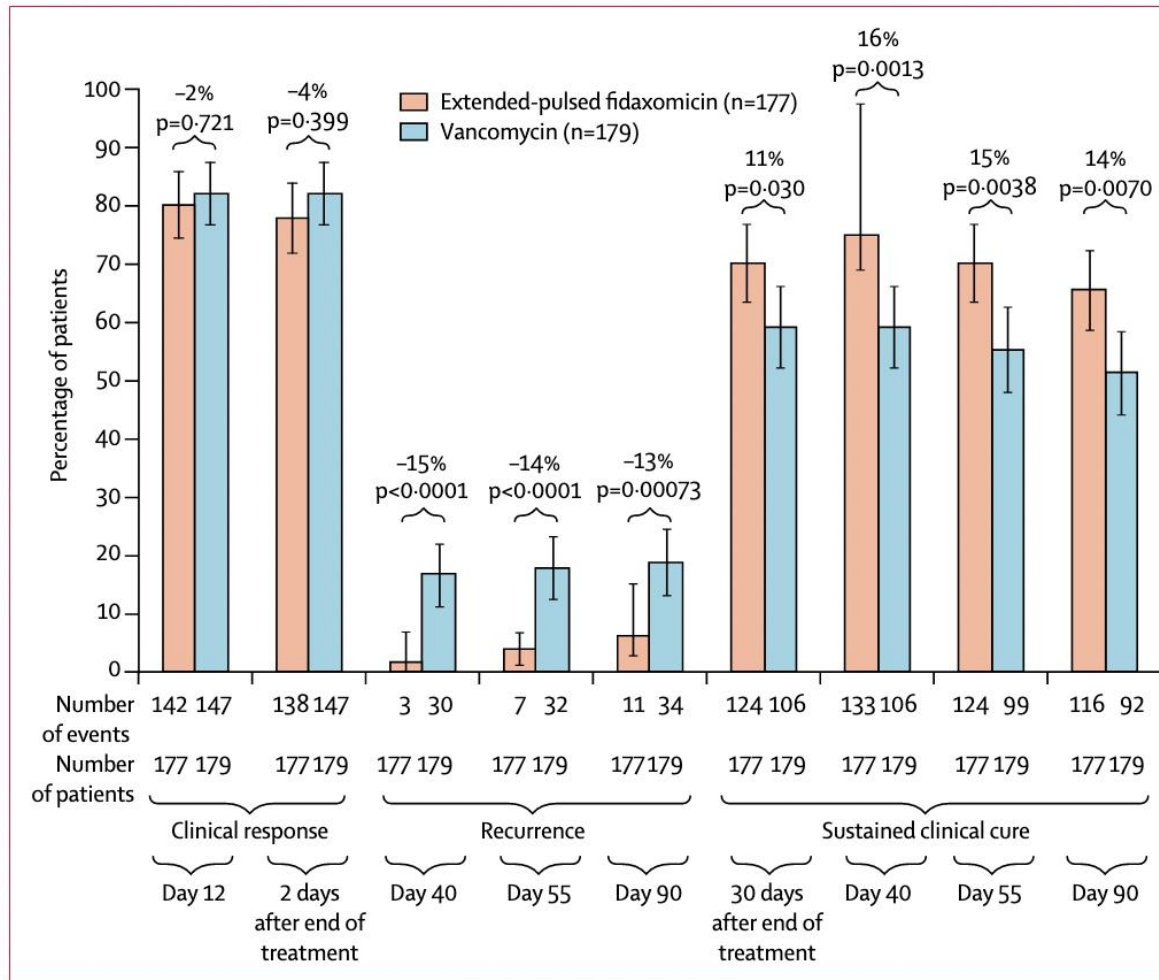
1 Identifier les patients qui vont récidiver

2 Comment optimiser le traitement de première ligne ?

3 Quelles solutions chez les récidivistes ?



Antibiothérapies prolongées ?



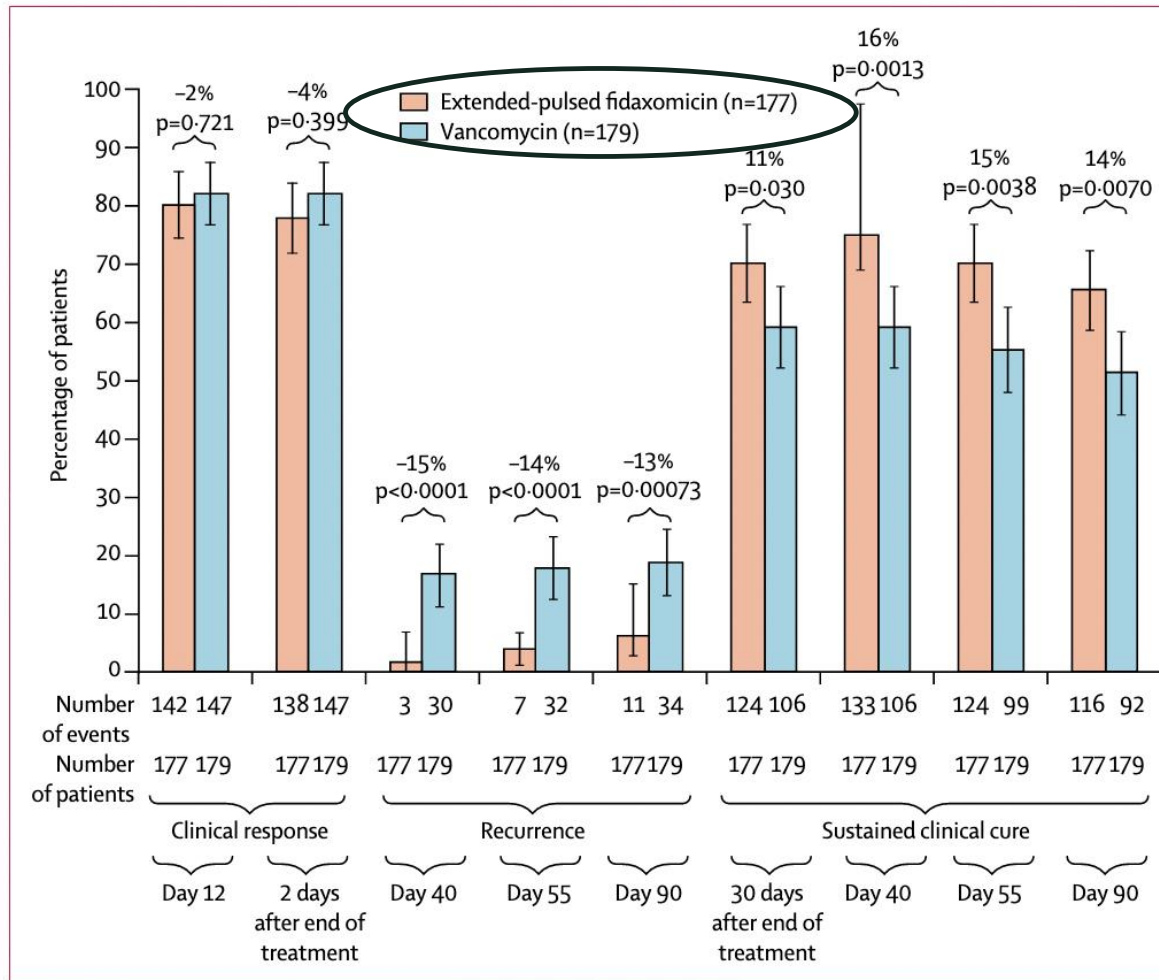
Fidaxomyne – Protocole EXTEND

200mg * 2 / jour pendant 5 jours puis
200mg/48h pendant 20 jours (10 prises)

Figure 2: Selected clinical outcomes

Bars show 95% CI. Percentage increase or decrease for extended-pulsed fidaxomicin compared with vancomycin is shown above each pair of bars.

Antibiothérapies prolongées ?



Fidaxomycline – Protocole EXTEND

200mg * 2 / jour pendant 5 jours puis
200mg/48h pendant 20 jours (10 prises)

Figure 2: Selected clinical outcomes

Bars show 95% CI. Percentage increase or decrease for extended-pulsed fidaxomicin compared with vancomycin is shown above each pair of bars.

Antibiothérapies prolongées ?

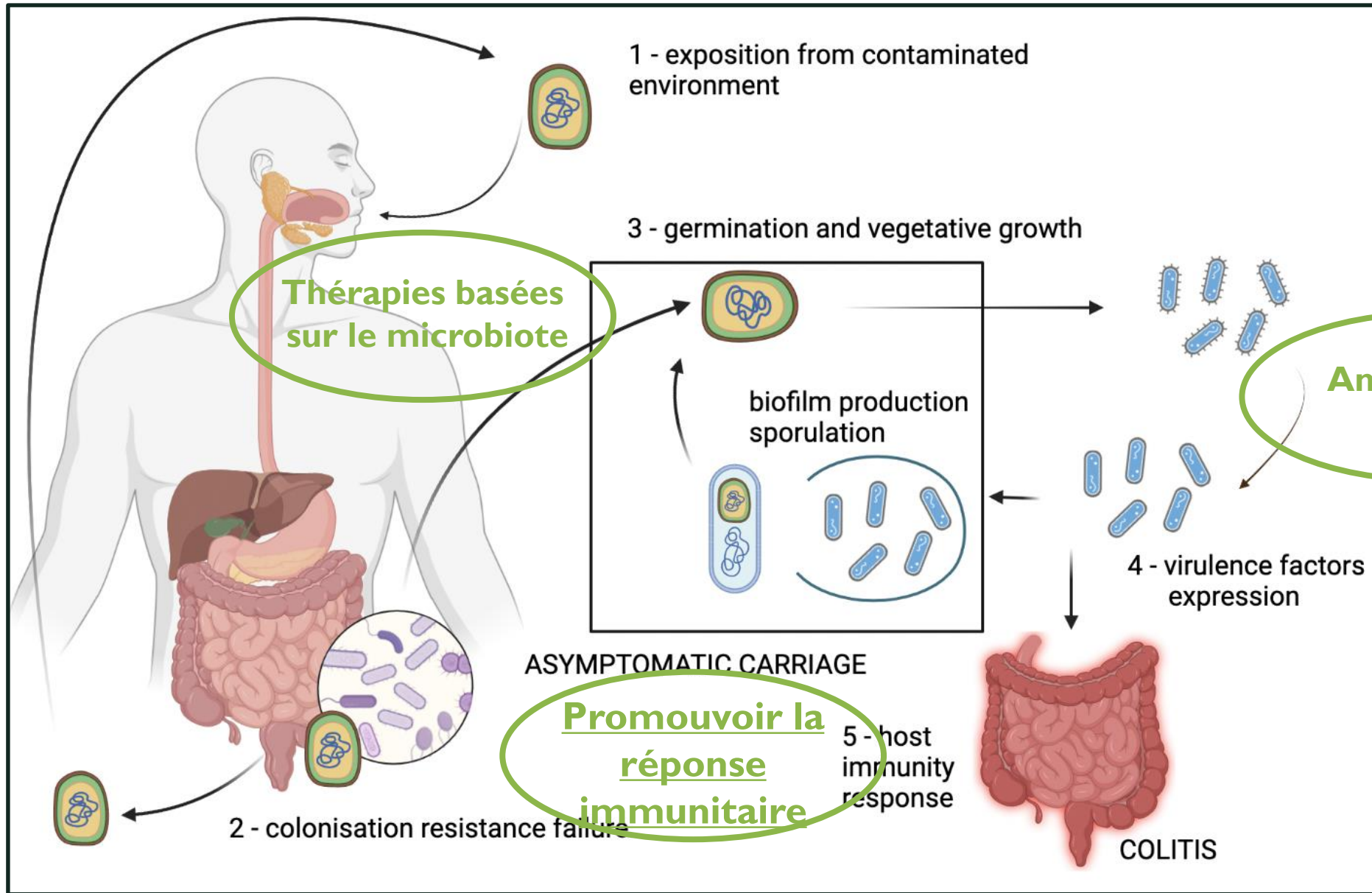
Table 1. Guideline recommendations for extended duration vancomycin therapy.

Source	Acute	Extended
SHEA/IDSA ⁵	125 mg four times daily × 10–14 days	125 mg BID × 1 week, 125 mg daily × 1 week, then 125 mg every 48 or 72 h × 2–8 weeks
ESCMID ⁶	125 mg four times daily × 10 days	125–500 mg daily pulsed every 48–72 h × 3 weeks minimum
ASID ⁷	125 mg four times daily × 14 days	125 mg BID × 1 week, then 125 mg every 48 h × 2–8 weeks
ACG ⁸	125 mg four times daily × 10 days	125 mg daily pulsed every 72 h × 10 doses

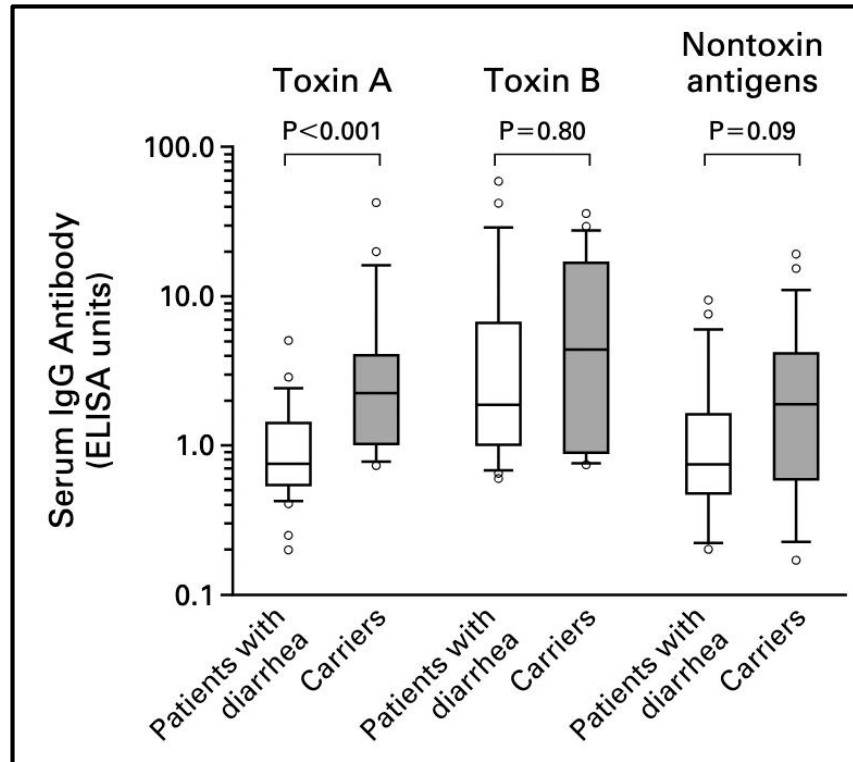
ACG, American College of Gastroenterology; ASID, Australasian Society of Infectious Diseases; BID, twice daily; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; IDSA, Infectious Disease Society of America; SHEA, Society for Healthcare Epidemiology of America.

= avis d'experts

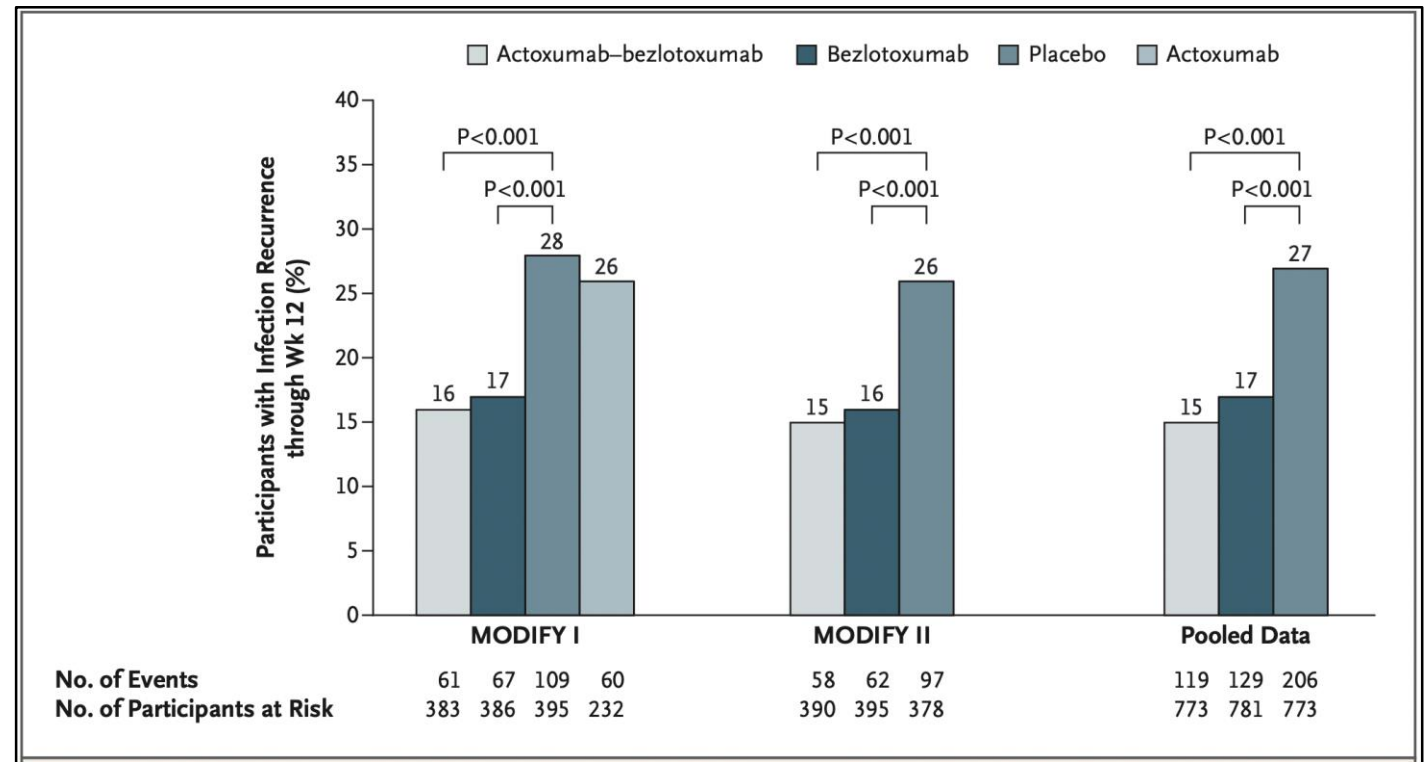
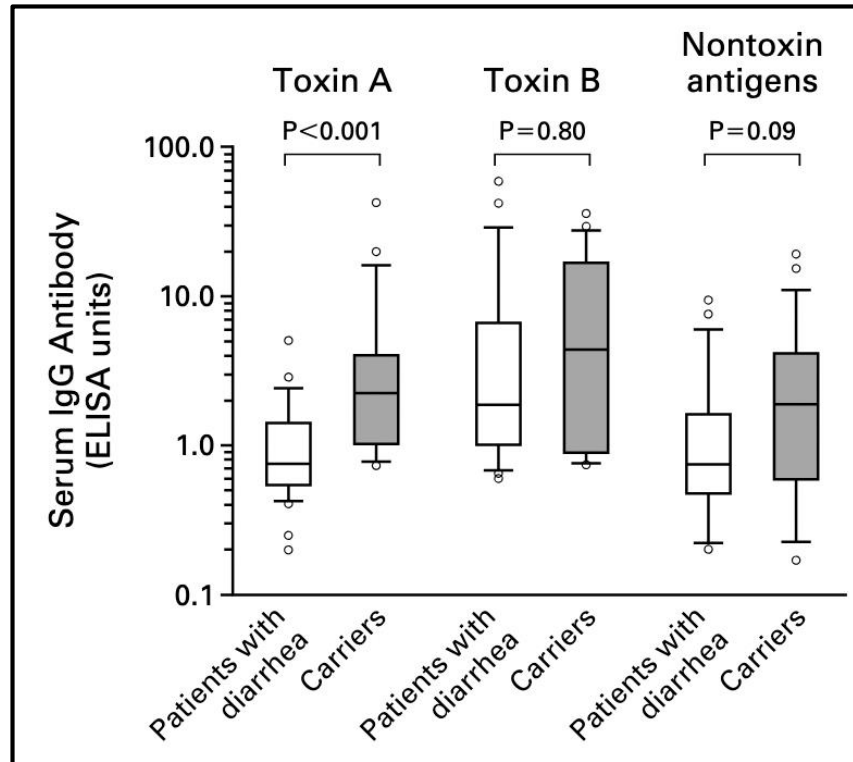
1 RCT versus FMT (critère de jugement biologique)



Bezlotoxumab : Un anticorps monoclonal anti-toxine B

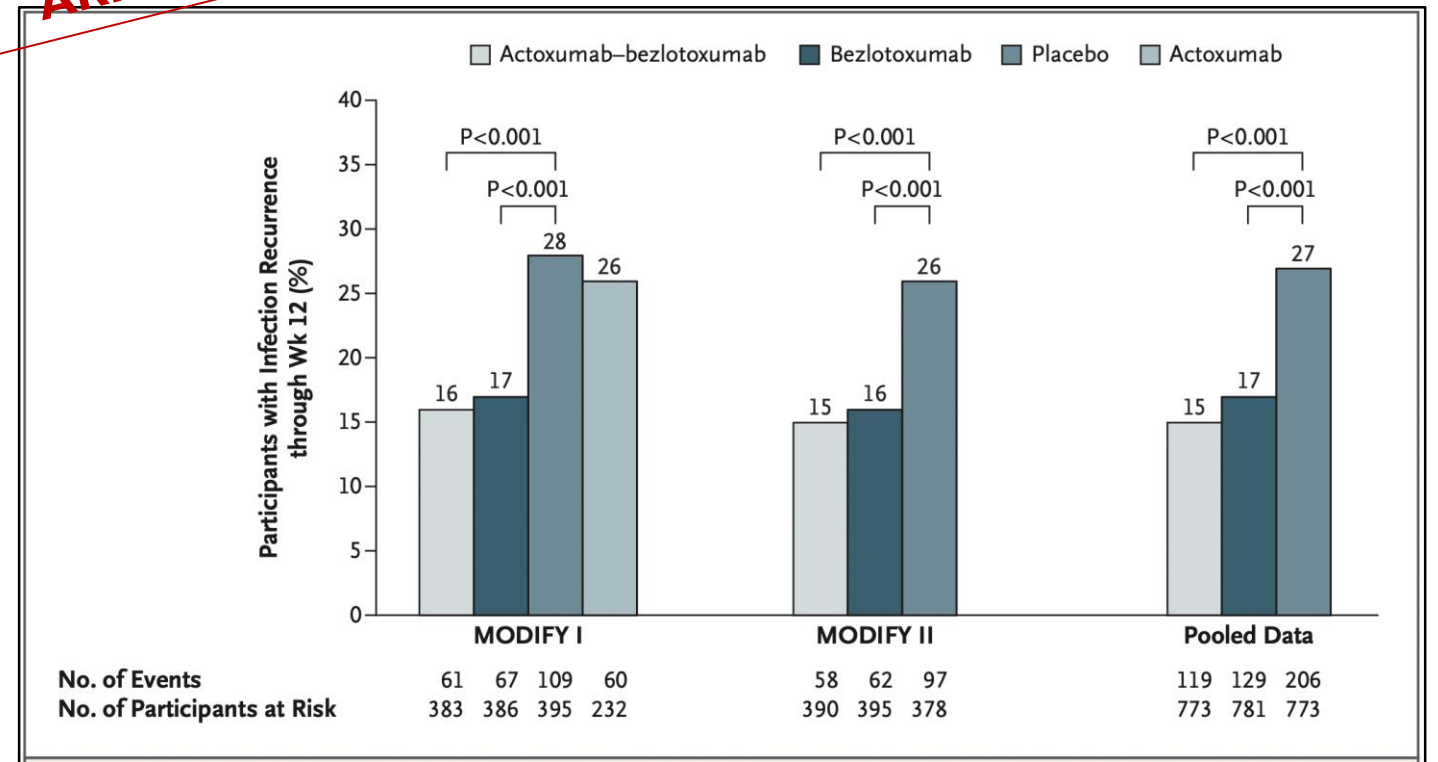
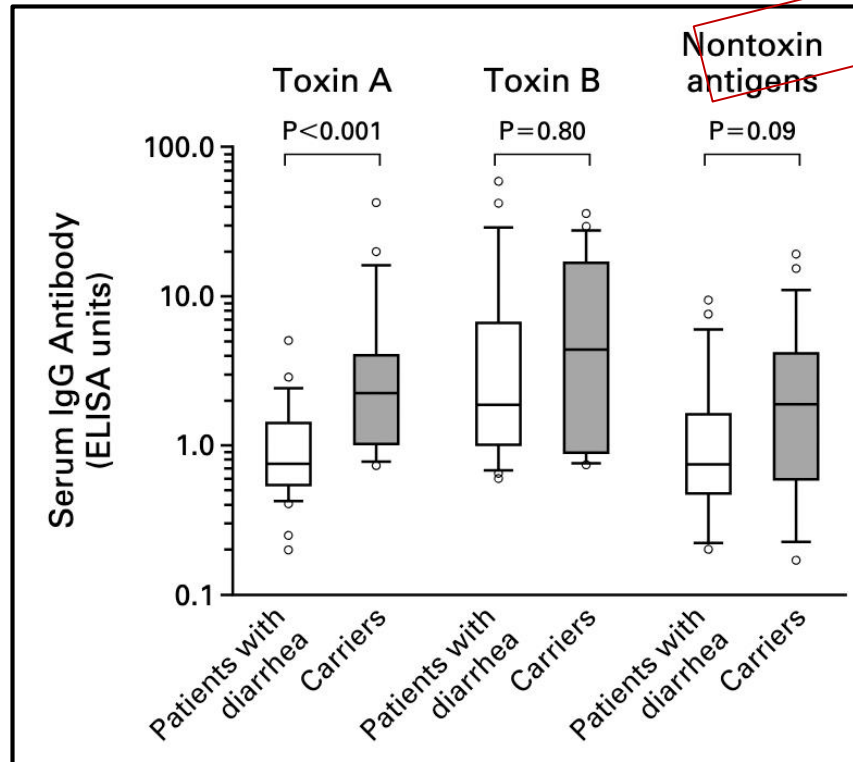


Bezlotoxumab : Un anticorps monoclonal anti-toxine B



Bezlotoxumab : Un anticorps monoclonal anti-toxine B

ARRET DE COMMERCIALISATION ANNOUNCE



Un vaccin ? Des résultats en attente ...

Completed ⓘ

Clostridium Difficile Vaccine Efficacy Trial (Clover)

ClinicalTrials.gov ID ⓘ NCT03090191

Sponsor ⓘ Pfizer

Information provided by ⓘ Pfizer (Responsible Party)

Last Update Posted ⓘ 2023-02-13



Un vaccin ? Des résultats en attente ...



Completed i

Clostridium Difficile Vaccine Efficacy Trial (Clover)

ClinicalTrials.gov ID i NCT03090191

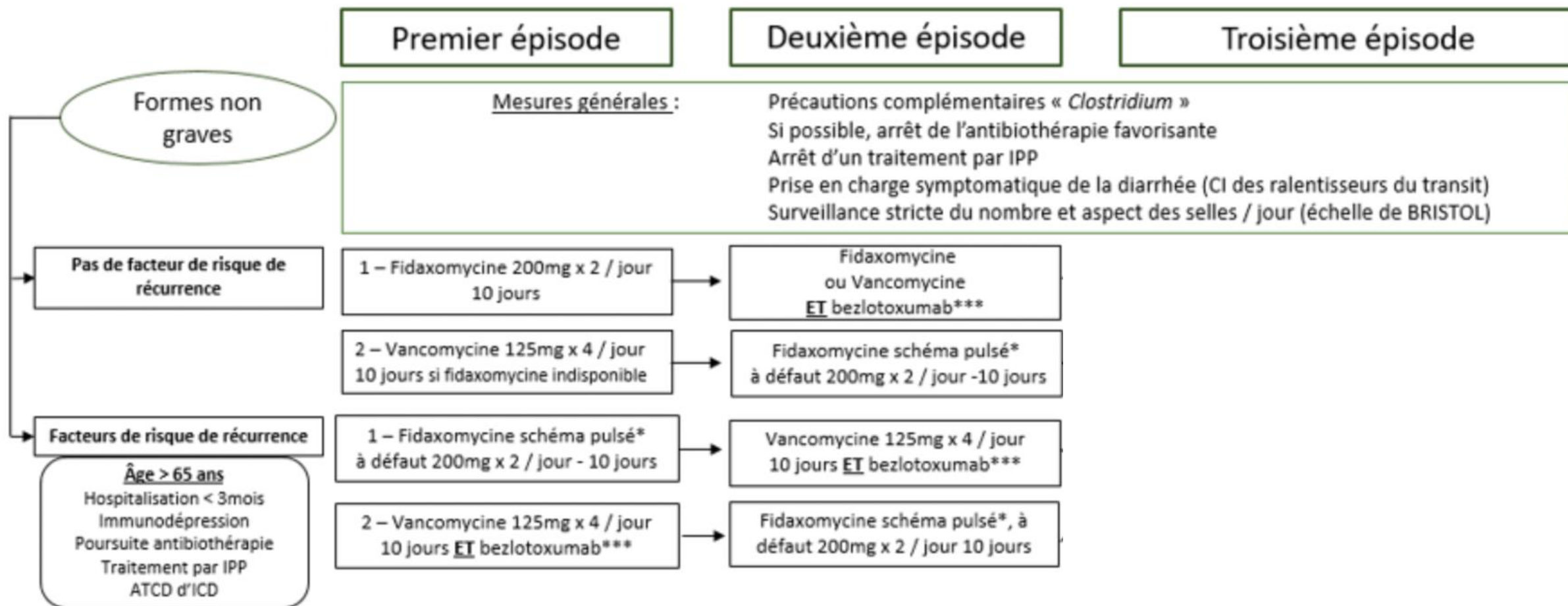
Sponsor i Pfizer

Information provided by i Pfizer (Responsible Party)

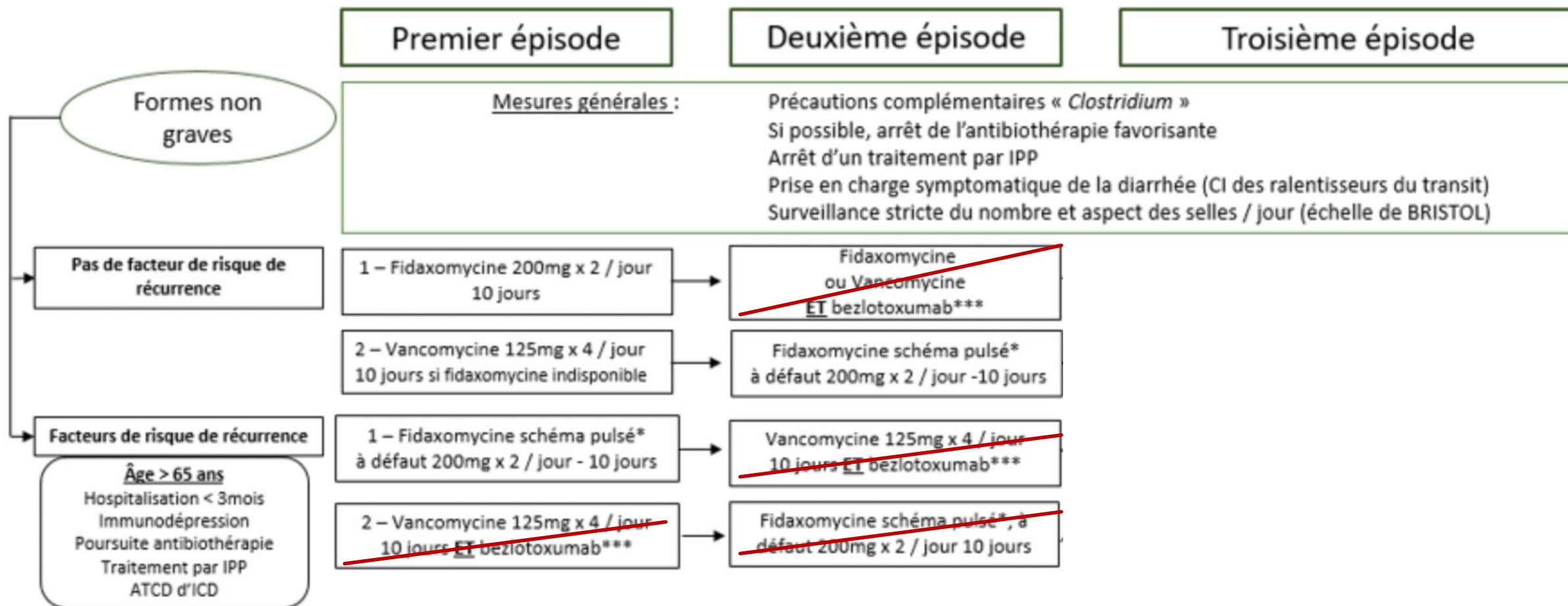
Last Update Posted i 2023-02-13

	Clostridium Difficile Vaccine	Placebo
	Participants were randomized to Clostridium difficile vaccine 200 microgram total toxoid per dose intramuscularly at Months 0, 1 and 6.	Participants were randomized to placebo (normal saline solution of 0.9 percent [%] sodium chloride) intramuscularly at Months 0, 1 and 6.
Overall Number of Participants Analyzed	7707	7805
Measure Type: Number Unit of Measure: Episodes	17	25
Method of Estimation		
Estimation Parameter	Vaccine efficacy	
Estimated Value	31.0	
Confidence Interval	(2-Sided) 96.4% -38.7 to 66.6	

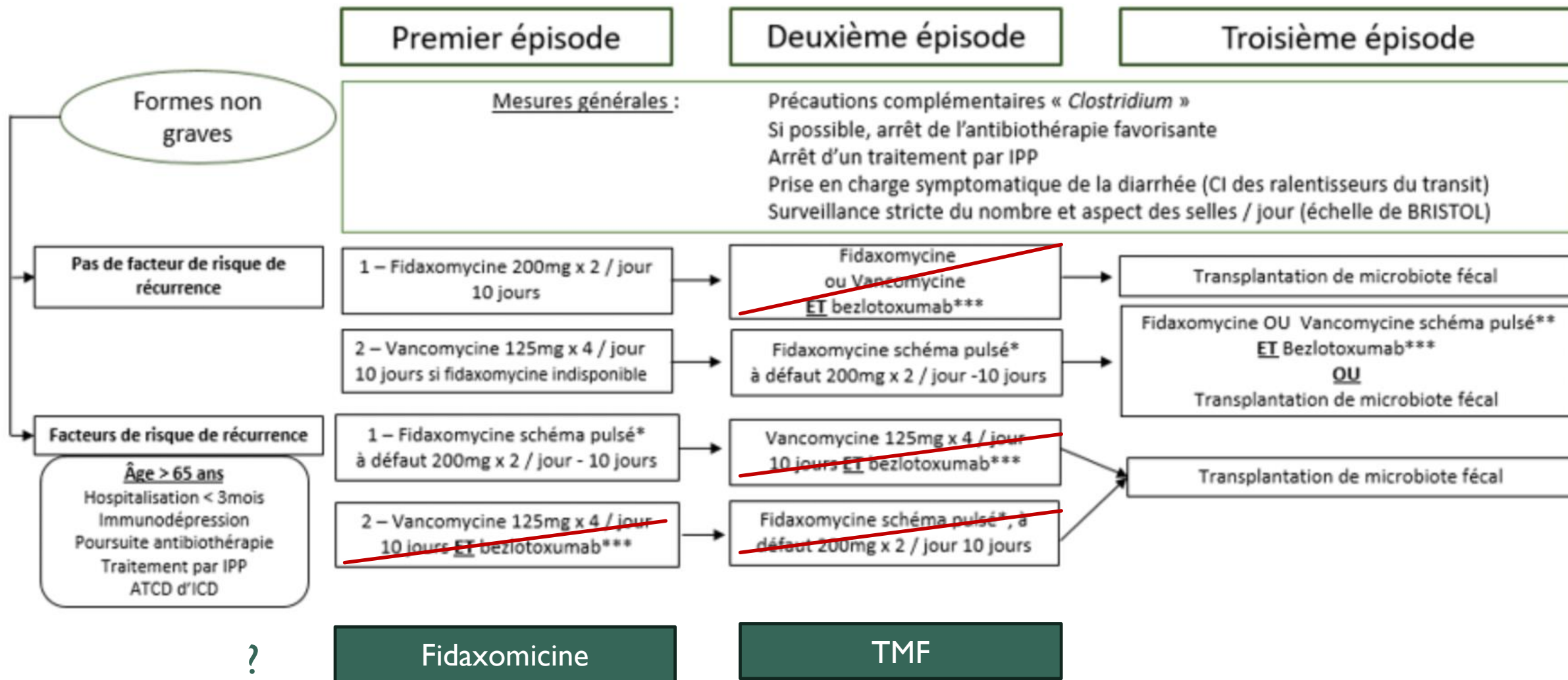
Protocole du CHU Lille - 2022

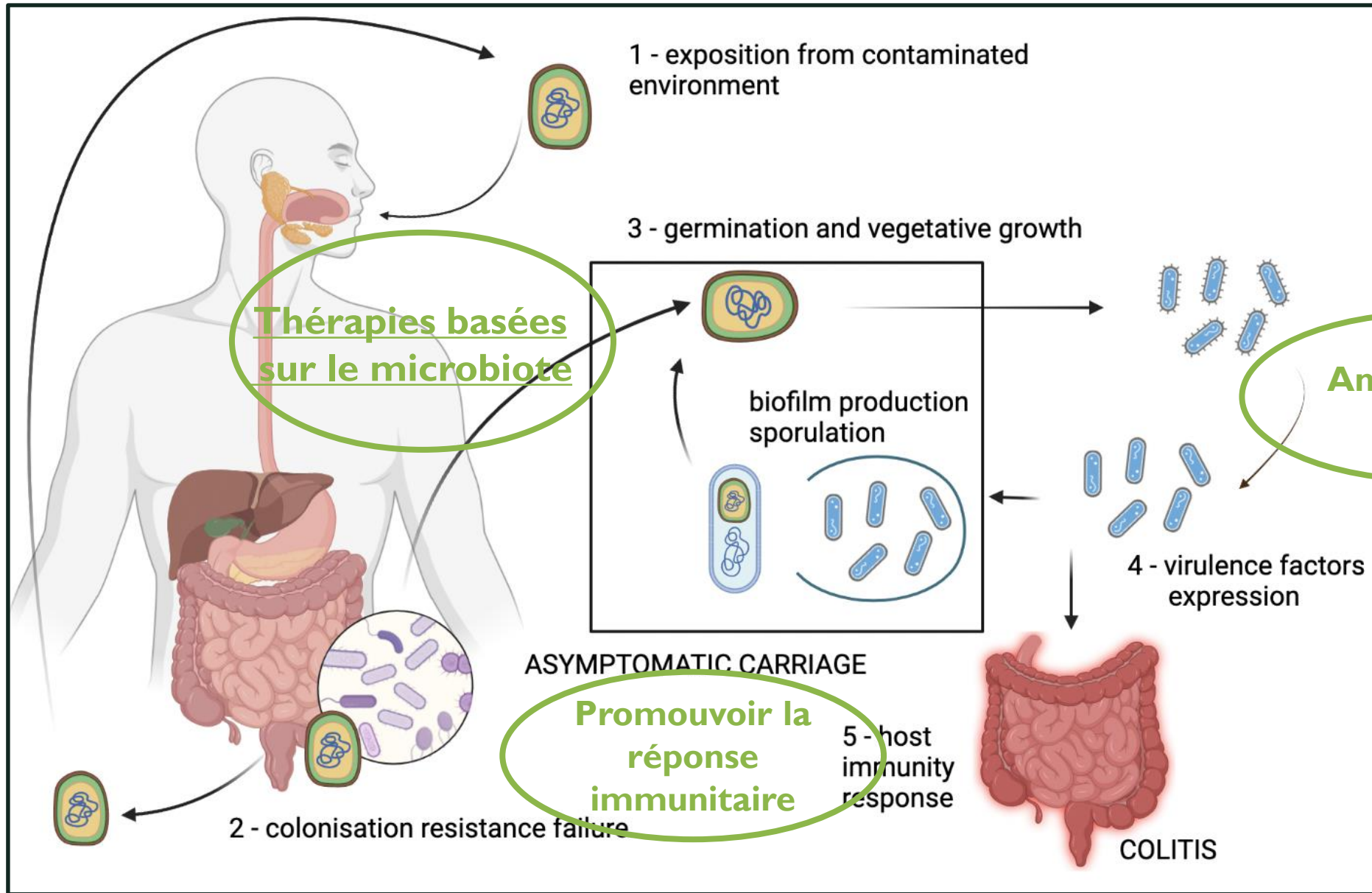


Protocole du CHU Lille - 2022



Protocole du CHU Lille - 2022





La transplantation de microbiote fécal : Essai PRINCEPS

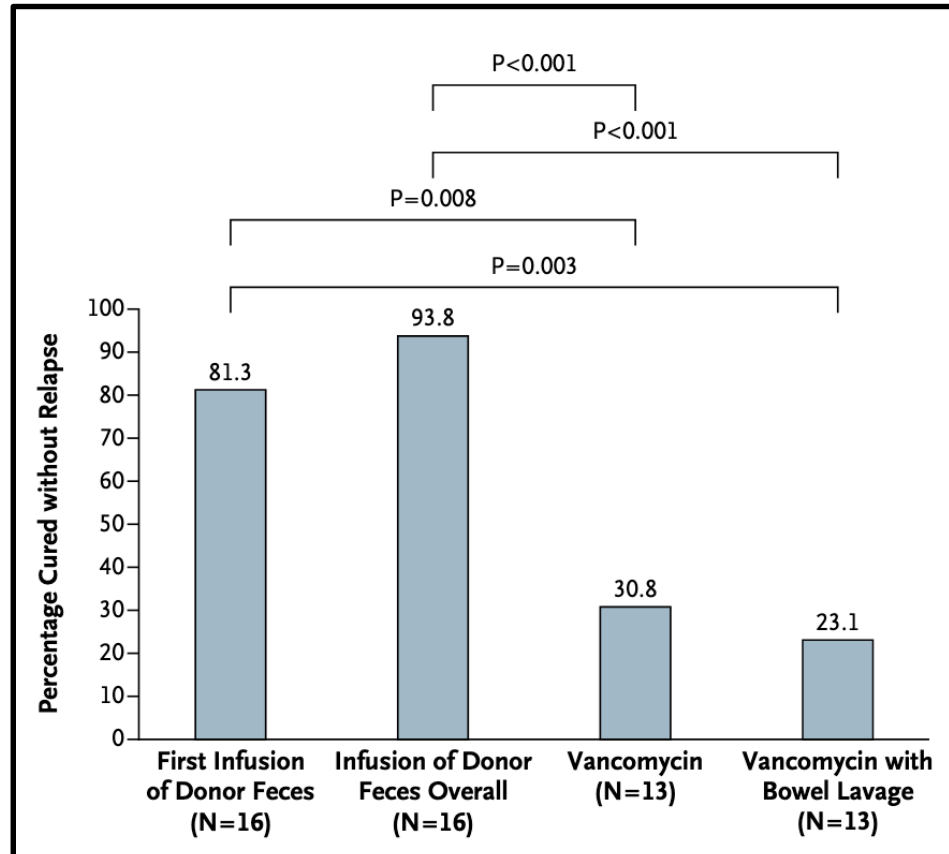


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

Shown are the proportions of patients who were cured by the infusion of donor feces (first infusion and overall results), by standard vancomycin therapy, and by standard vancomycin therapy plus bowel lavage.

La transplantation de microbiote fécal : Essai PRINCEPS

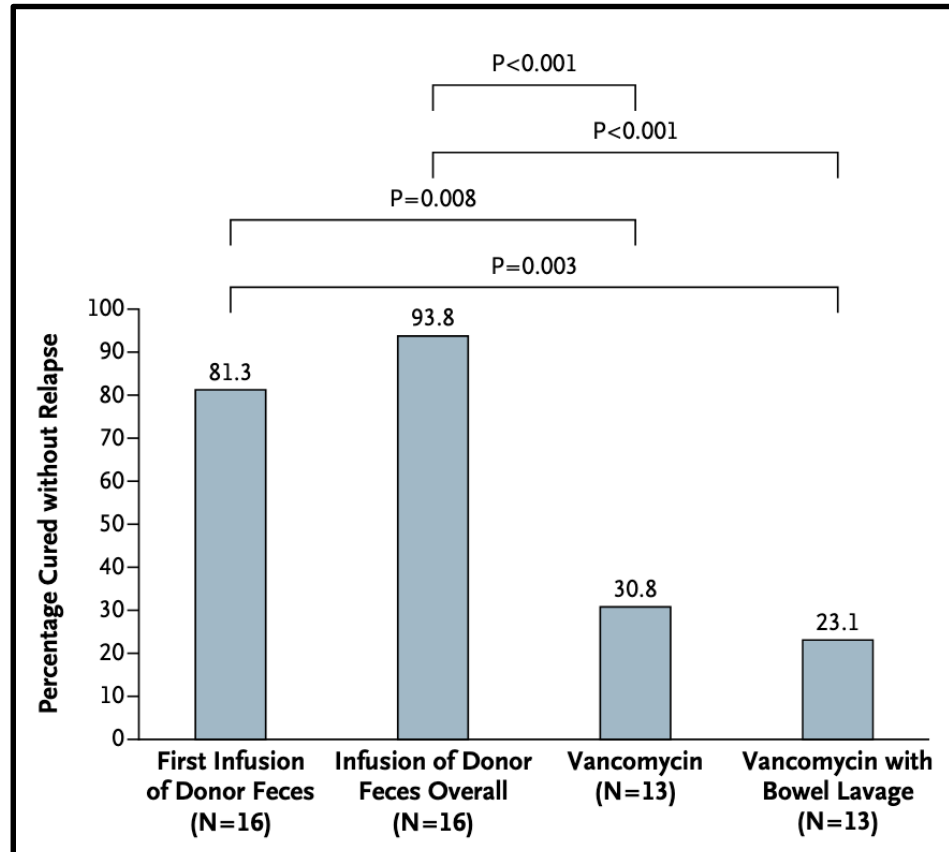


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

Shown are the proportions of patients who were cured by the infusion of donor feces (first infusion and overall results), by standard vancomycin therapy, and by standard vancomycin therapy plus bowel lavage.

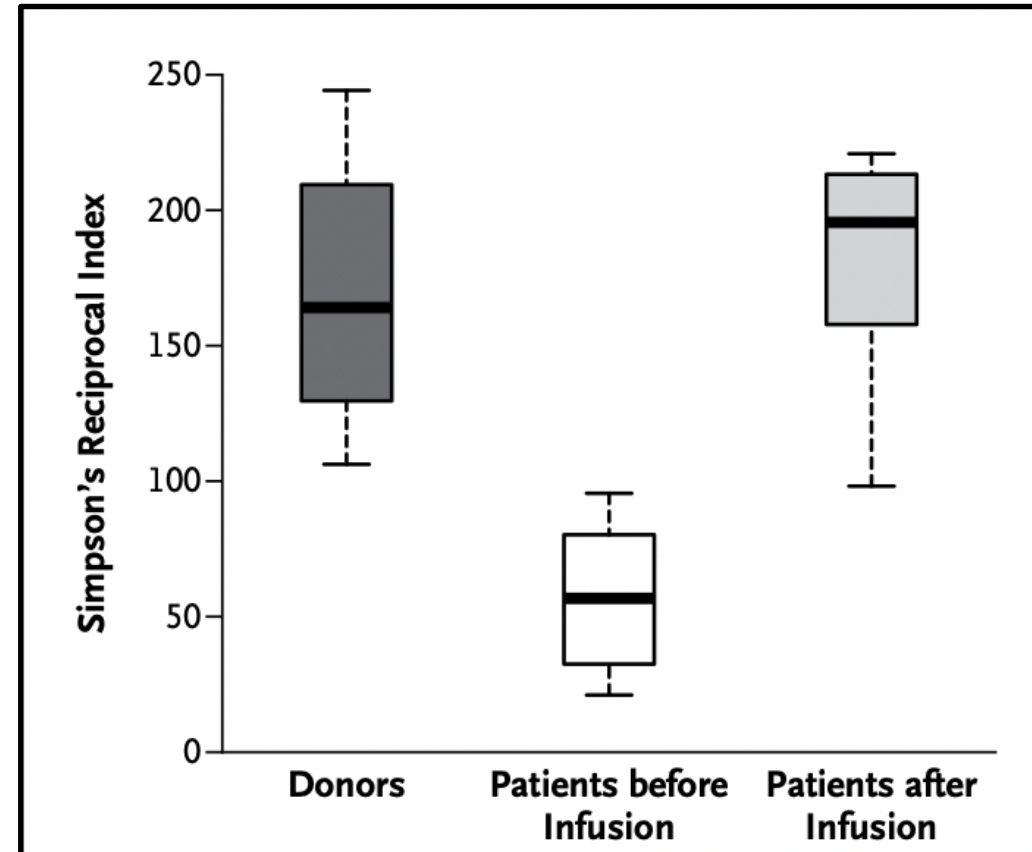


Figure 3. Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors.

La transplantation de microbiote fécal : Essai PRINCEPS

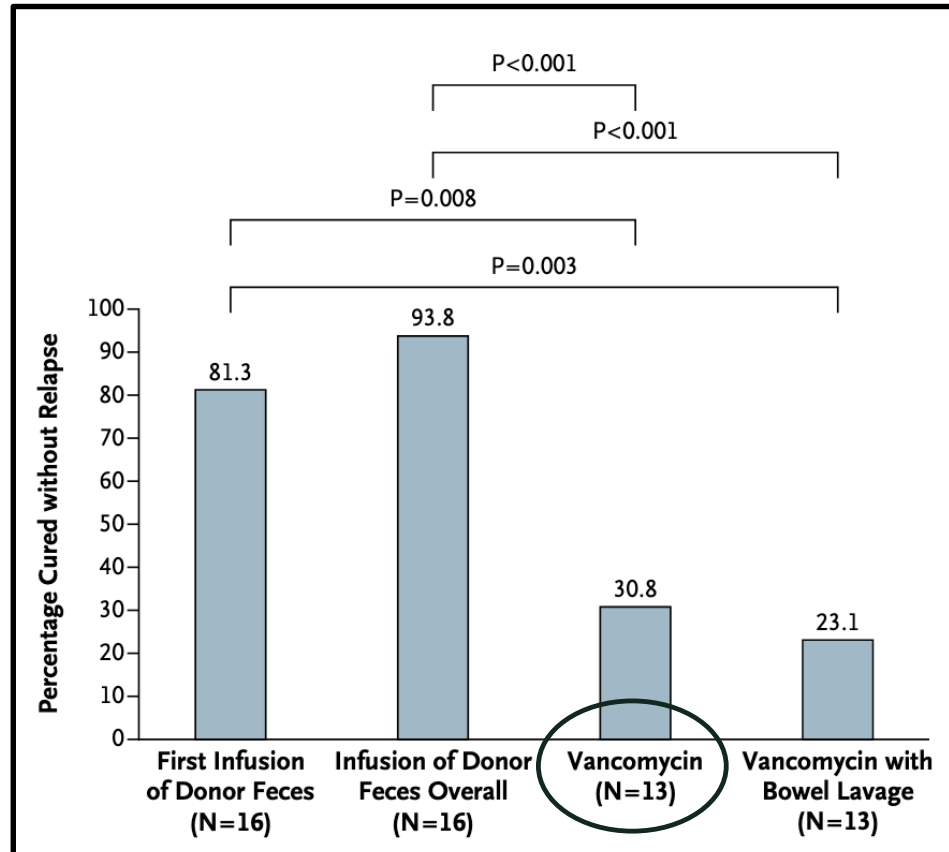


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

Shown are the proportions of patients who were cured by the infusion of donor feces (first infusion and overall results), by standard vancomycin therapy, and by standard vancomycin therapy plus bowel lavage.

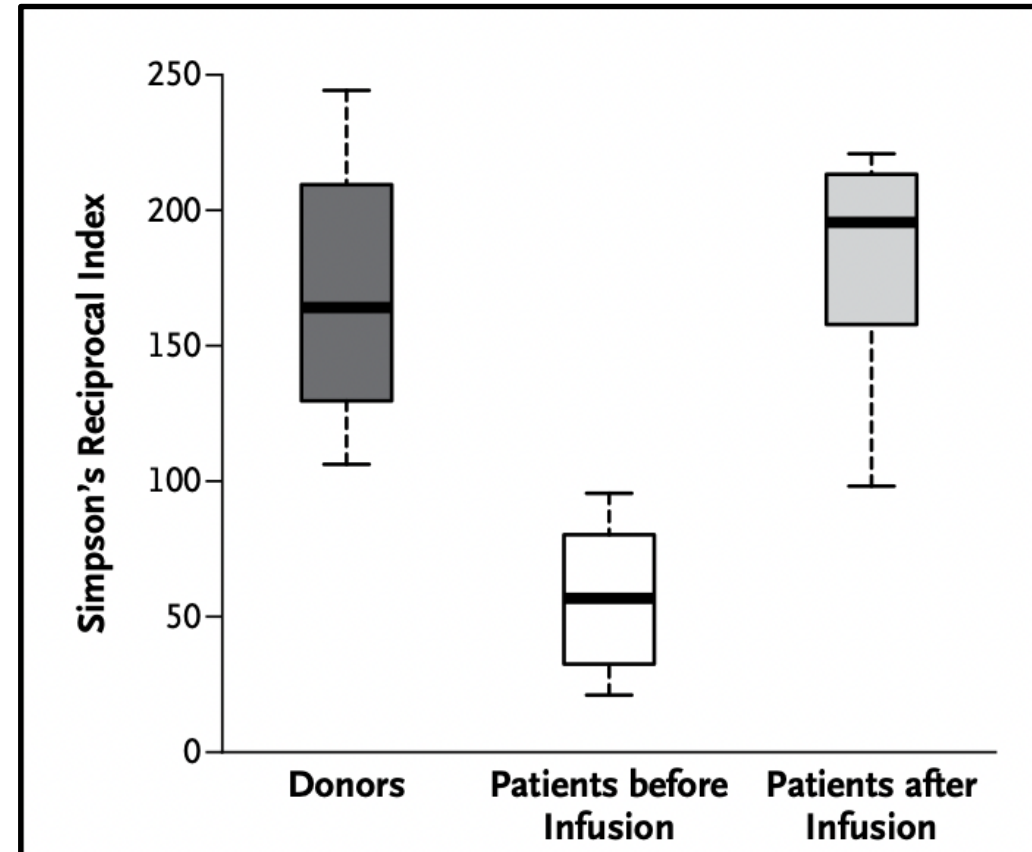
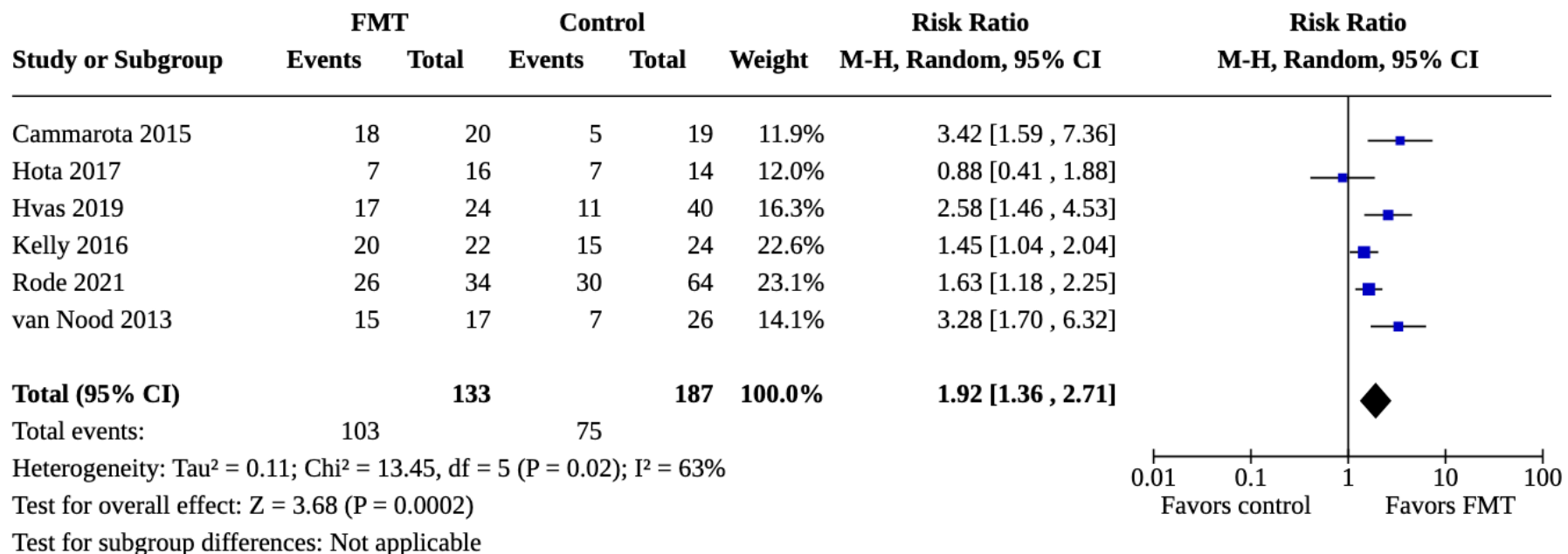


Figure 3. Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors.

La TMF : méta-analyse Cochrane

Analysis 1.1. Comparison 1: Fecal microbiota transplantation (FMT) versus control for the treatment of recurrent *Clostridioides difficile* infections (rCDI), Outcome 1: Resolution of rCDI: intention-to-treat analysis



La TMF versus la fidaxomicine ?

Fecal microbiota transplantation (FMT) vs fidaxomicin vs vancomycin for recurrent *Clostridium difficile* infection (CDI)

OPEN LABEL, SINGLE-CENTER, RANDOMIZED CLINICAL TRIAL

64 patients with rCDI

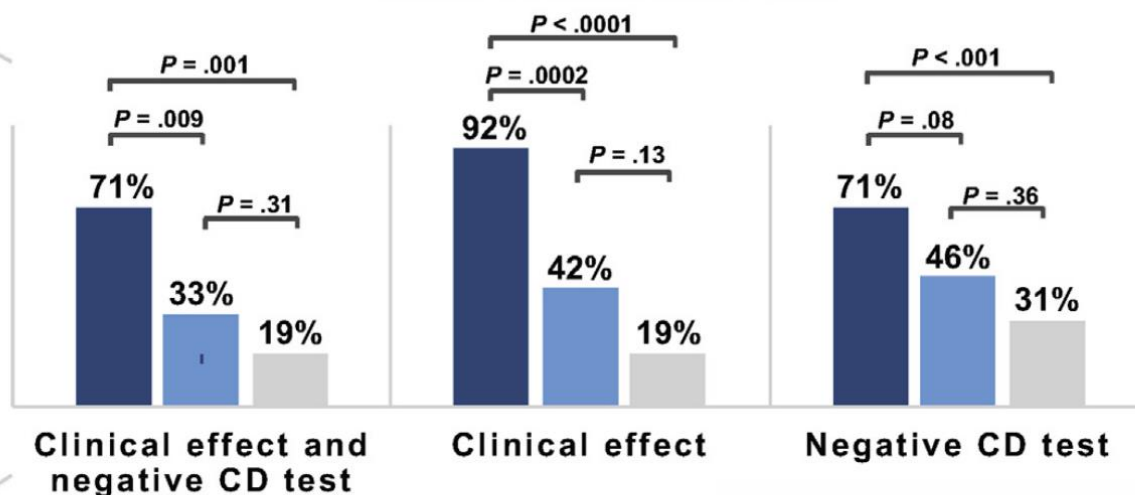


FMT (n = 24)
Après 4 à 10 jours de Vanco

Fidaxomicin (n = 24)

Vancomycin (n = 16)

Week 8 resolution rates



Gastroenterology

La TMF versus la fidaxomicine ?

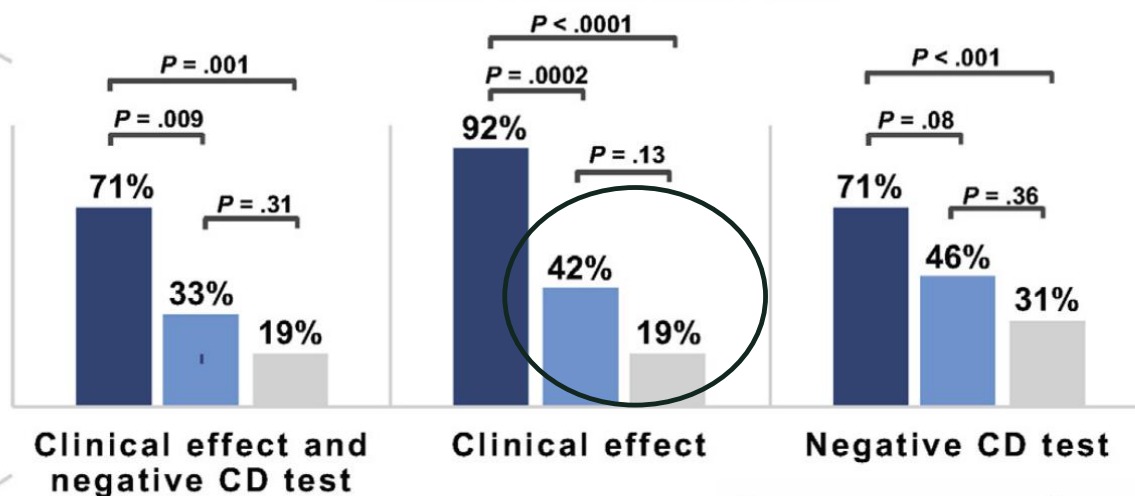
Fecal microbiota transplantation (FMT) vs fidaxomicin vs vancomycin for recurrent *Clostridium difficile* infection (CDI)

OPEN LABEL, SINGLE-CENTER, RANDOMIZED CLINICAL TRIAL

64 patients with rCDI

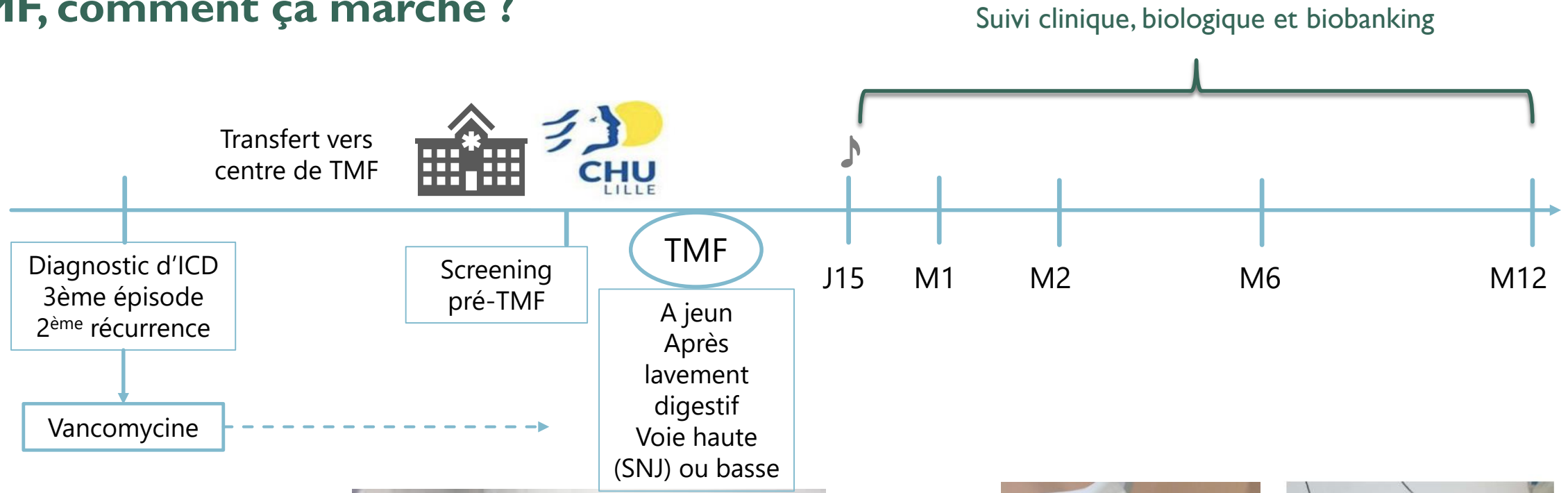


Week 8 resolution rates

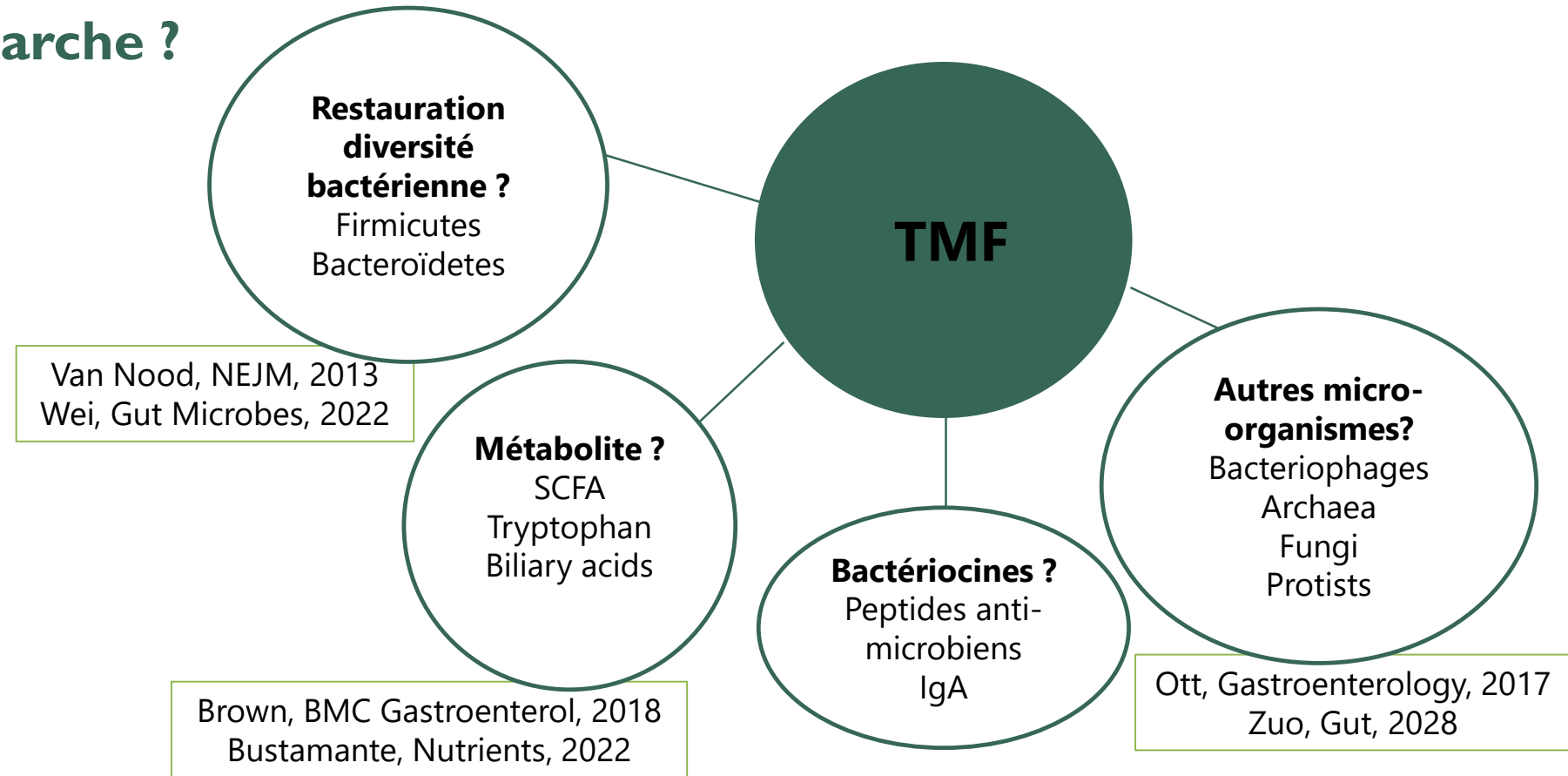


Gastroenterology

TMF, comment ça marche ?



TMF, comment ça marche ?



↳ Recherche de thérapie ciblée contre l'infection à *Clostridioïdes difficile*

Vers des thérapies ciblées basées sur le microbiote



- Spores de Firmicutes purifiées
- Issues de donneur
- Conditionnement en comprimés

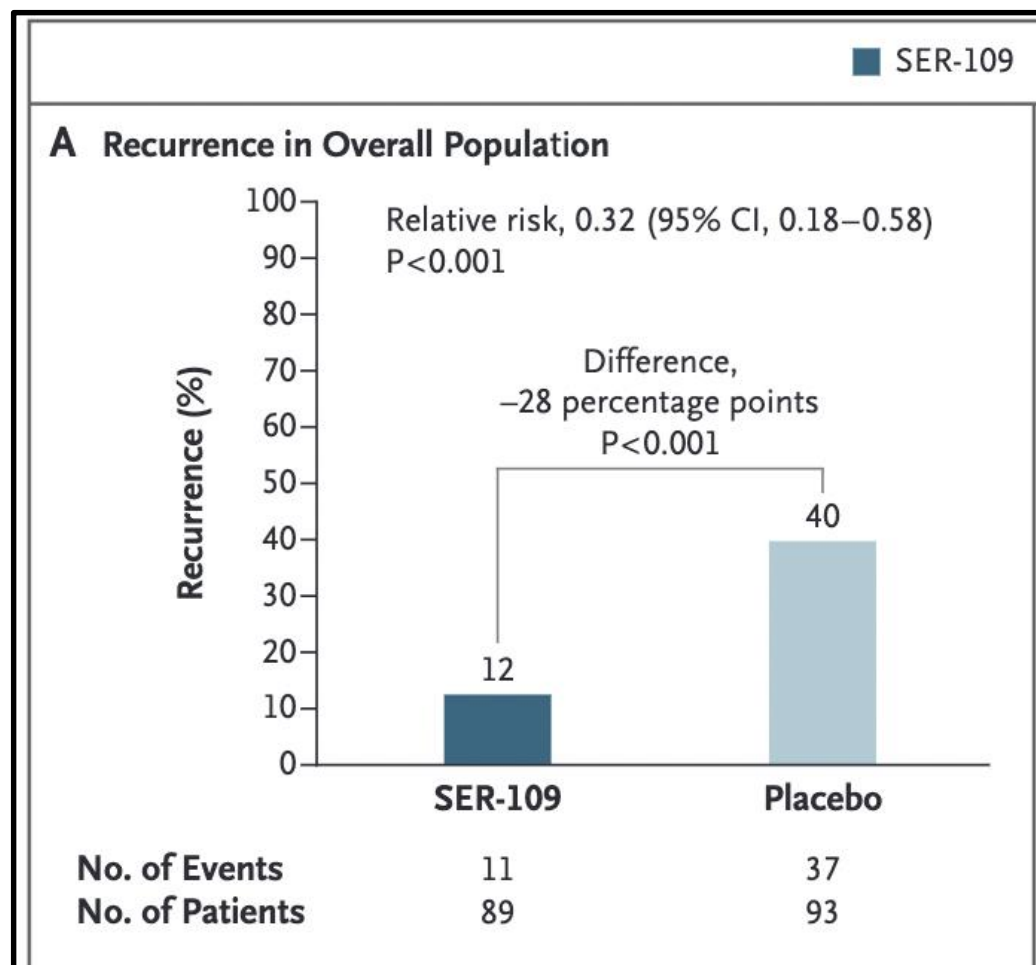
Critères d'inclusion

Personnes adultes > 18 ans

≥ 3 épisodes d'ICD dans les 12 derniers mois

Randomisation 1 : 1 = placebo ou SER-109

4 gélules, 1/j pendant 4j de suite



Conclusion

- **Un enjeu sur le traitement de première ligne**

Fidaxomicine	>	Vancomycine pour la prévention des récurrences
Fidaxomicine standard	?	Fidaxomicine EXTEND

- **Peu de ressources thérapeutiques par la suite hors TMF**

- **Enjeux de recherche sont le développement de thérapies basées sur le microbiote en prévention secondaire**



MERCI POUR VOTRE ATTENTION



Faut-il proposer une antibioprophylaxie ? Des données retrospectives

Table 1. Summary of Data on *Clostridioides difficile* Infection Prophylaxis

Reference	Design	Patient Population	OVP Dose	Results
Van Hise et al 2016 [13]	Retrospective cohort	Adults (aged ≥18 years) with history of CDI subsequently hospitalized and treated with systemic antimicrobial therapy/secondary prophylaxis	125 mg or 250 mg twice daily	CDI recurrence in OVP group 4.2% vs control group 26.6% ($P < .001$)
Carignan et al 2016 [14]	Retrospective cohort	Adults (aged ≥18 years) who received antibiotics within 90 days of initial or recurrent CDI/secondary prophylaxis	125 mg 4 times daily (84%)	OVP effective only in those with history of recurrent CDI (adjusted hazard ratio, 0.47; $P < .0001$)
Splinter et al 2018 [15]	Retrospective cohort	Adult (aged ≥18 years) renal transplant patients with a history of CDI/secondary prophylaxis	125 mg twice daily	CDI recurrence in OVP group 0% vs control group 8% ($P = .54$)
Knight et al 2019 [16]	Retrospective cohort	Adults (aged ≥18 years) with history of CDI subsequently hospitalized within 12 months and treated with systemic antimicrobial therapy/secondary prophylaxis	125 mg or 250 mg 4 times daily	CDI recurrence in OVP group 6.3% vs control group 28.8% ($P = .011$)
Zhang et al 2019 [17]	Retrospective cohort	Patients with history of recurrent CDI who refused, were not candidates for, or failed fecal microbiota transplantation who received systemic antimicrobial therapy/secondary prophylaxis	125 mg once daily after a 14-day treatment course of oral vancomycin	CDI recurrence occurred in 4 of 13 (31%) within 8 weeks of OVP discontinuation
Papic et al 2018 [18]	Retrospective cohort	Adults (aged ≥65 years) hospitalized ≥72 hours who received parenteral antibiotics for ≥24 hours/primary prophylaxis	125 mg once daily	CDI occurrence in OVP group 0% vs control group 10.4% ($P = .0022$)
Ganetsky et al 2018 [19]	Retrospective cohort	All adult allogeneic hematopoietic cell transplantation patients during study period/primary prophylaxis	125 mg twice daily for duration of stay	CDI in-hospital occurrence in OVP group 0% vs control group 20% ($P < .001$)
Caroff et al 2019 [20]	Retrospective cohort	Adult patients given at least 1 dose of systemic antibiotic with history of CDI in previous 30–150 days/secondary prophylaxis	Unknown	CDI recurrence in OVP group 9.8% vs control group 9.4% (odds ratio, 1.06; 95% confidence interval, 0.60–1.81)

Abbreviations: CDI, *Clostridioides difficile* infection; OVP, oral vancomycin prophylaxis.

Faut-il proposer une antibioprophylaxie ? Un essai randomisé

Monocentric randomized open label trial

Patients were considered **high-risk** for CDI with the following:

Aged ≥ 60 years,

Hospitalized ≤ 30 days prior to the index hospitalization

Received systemic antibiotics during prior hospitalization

Targeted (high-risk) patients who were currently receiving systemic antibiotics (defined as > 1 dose of a systemic antibiotic) were identified by utilization of a computer-based risk-prediction model

100 patients were evaluated

50 patients were randomized in each arm

Vancomycine [125mg/day until 5 dayx after ATB discontinuation]

Vs Placebo

Table 3. Efficacy of Oral Vancomycin Prophylaxis

Outcome	Cases, n (50)	Controls, n (50)	PValue
Healthcare facility–onset <i>Clostridioides difficile</i> infection	0	6	.03
Community-onset, healthcare facility-associated <i>C. difficile</i> infection	0	2	.49



Pas de dépistage des ERV



Stratégie jugée coût efficace