Probiotiques et infections,
Un sujet « incertain… »

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Toi aussi, ils t'ont mis au régime bière, choucroute, yaourt ?
M'en parle pas ! Ces probiotiques m'ont foutu de ces allergies !!
Allergie France ©

So, a strict roadmad….

- General :
  - Definition, Market
- Recent findings in :
  - Infectious diarrhea, *C. dif*, VRE, UTI, VAP, Pediatrics, Acute pancreatis
- Recent opinions, caveat and soforth.

Definition and market

- « Life microbial supplement that beneficially affect the consumer by improving intestinal microbial balance ».
- Vague and uncertain alledged properties
- Drug or food : you never know…
- Multiple strains of various species
- No strain-specific properties requested

Big and highly dynamic buissenness…

Western Europe: Consumer market for probiotic and prebiotic products, 2000 to 2010

Market value (€m)

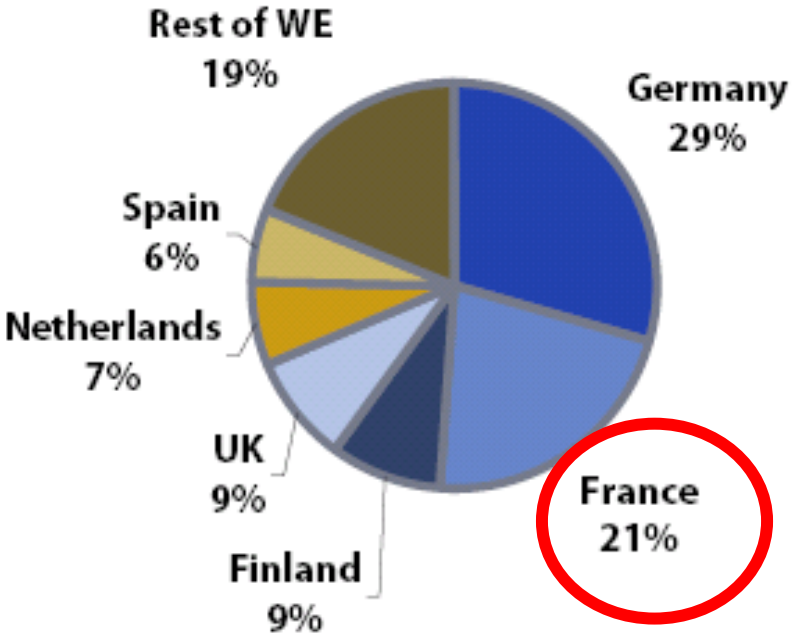
	2000	2005p	cagr 00-05	2010f	cagr 05-10
Probiotics	824.2	1,447.1	11.9%	2,100.4	7.7%
Prebiotics	365.3	878.6	19.2%	1,370.6	9.3%

Source RTS Resource Ltd

By comparison antibiotic market in Eu ~7.000€m (source IMS)

Western Europe: Share of market for probiotics as industrial food ingredient by main country, 2005

% Share of market value (€m)



A pattern very different from antibiotics : Germany 50% of French use

Source RTS Resource Ltd

CDAD, and Acute Infectious diarrhea,

It's hard to convince….

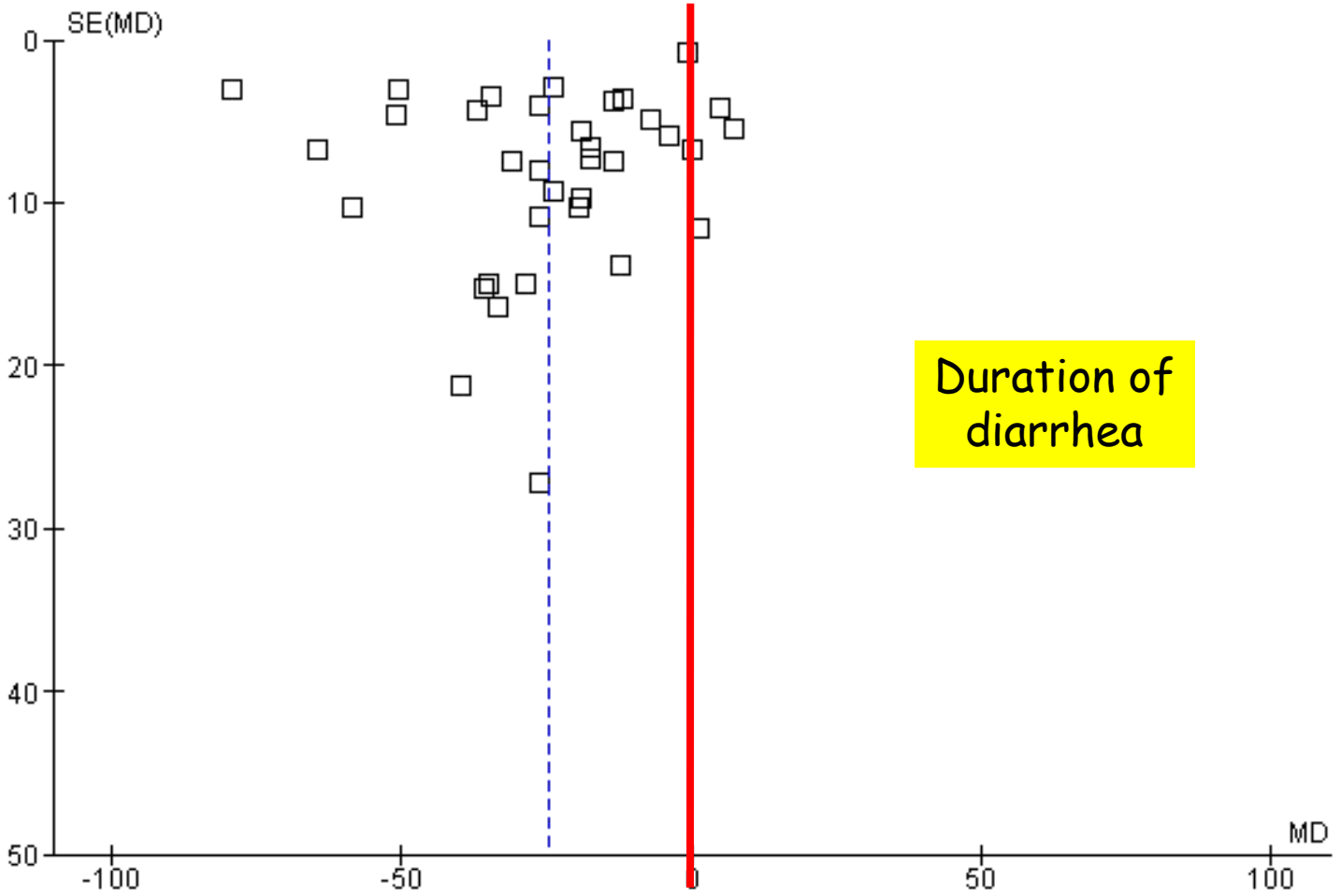
S. boulardii et *C.dif*

The most recent review

- 4 randomized, placebo-controlled studies
- Two for prevention of recurences
  - One reduction of relapses (RR=0.53; p<0.05)
  - One with trend in pts with high doses of vanco only (RR=0.33; p=0.05)
- Two for prevention after ATB Rx
  - Lack of power for significance
  - Increased risk of thirst and constipation

Tung JM *et al.* Can J gastroenterol, 2009

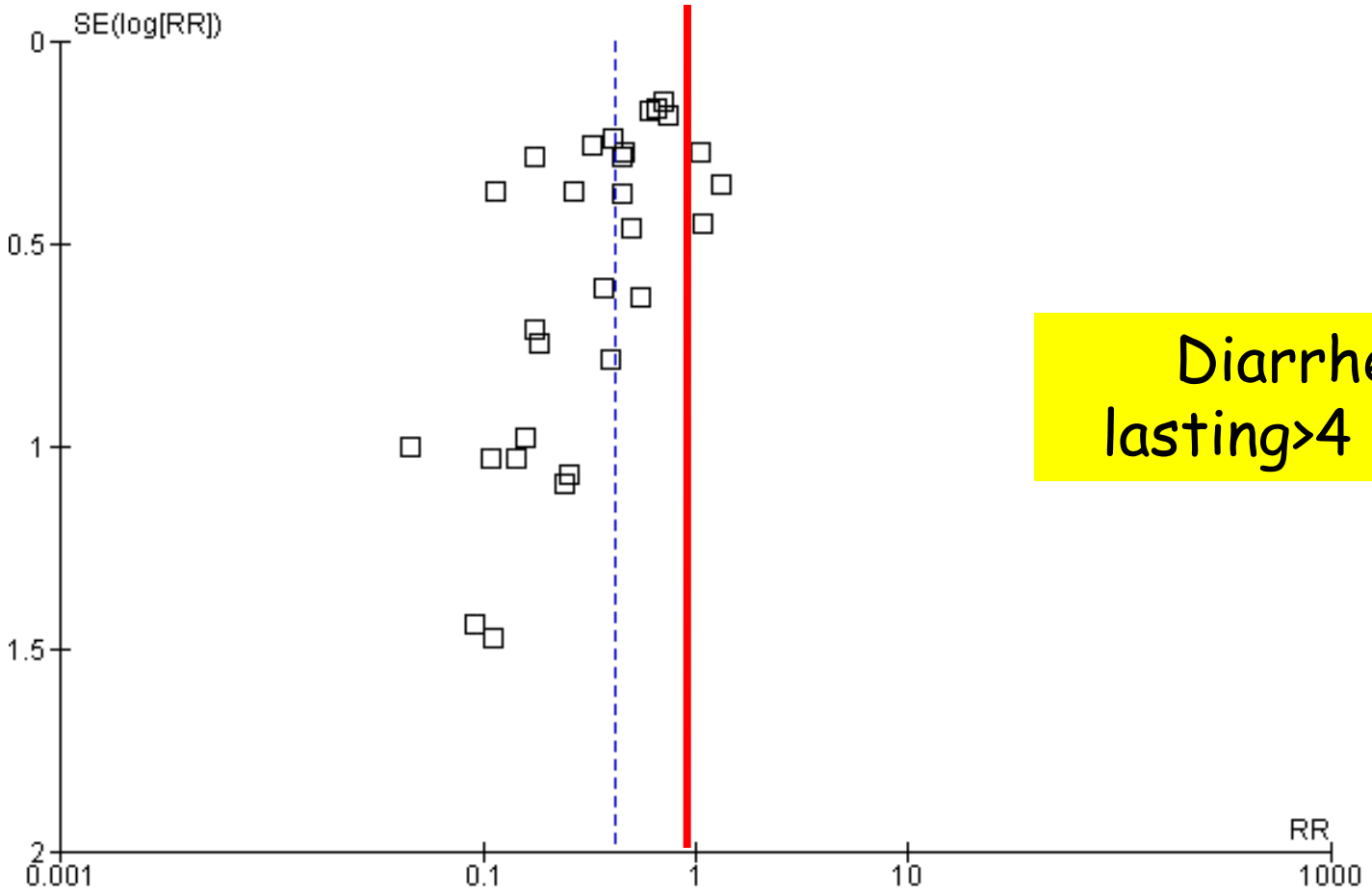
Probiotics for treating acute infectious diarrhea : a meta-analysis



Duration of diarrhea

Allen SJ *et al.*, The **Cochrane** Library 2010

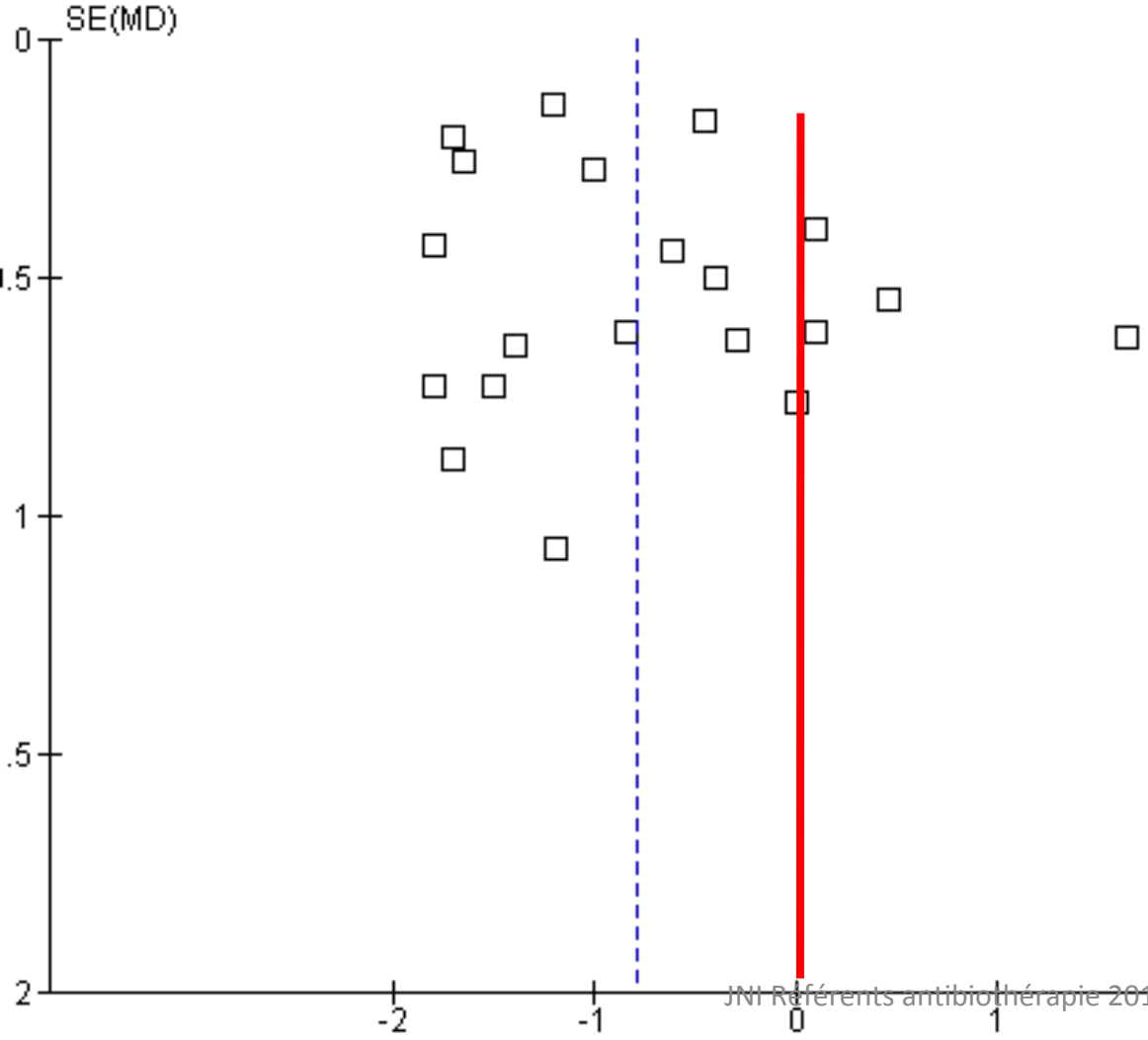
Probiotics for treating acute infectious diarrhea : a meta-analysis



Diarrhea lasting>4 days

Allen SJ *et al.*, The **Cochrane** Library 2010

Probiotics for treating acute infectious diarrhea : a meta-analysis



Mean stool frequency on day 2

Allen SJ *et al.*, The **Cochrane** Library 2010

But no differences in comparison between :

1. Strains (LGG, *Enterococcus*, *S. boulardii*)
2. Single organisms *vs* combinaitions
3. Live *vs* killed organisms
4. Dose (live organisms)
5. Severity of diarrhea (outpatients)
6. Mortality stratum in the countries where trials were undertaken

Allen SJ *et al.*, The **Cochrane** Library 2010

But no differences in comparison

✓ …safe and have clear beneficial effects in […] duration […]

✓ However, more research is needed to guide the use of particular probiotic regimens in specific patient groups.

Allen SJ *et al.*, The **Cochrane** Library 2010

Recurrent UTIs

A promising dawn ?

Rationales for prevention of rUTI with *L. crispatus*

- Vaginal colonisation a step for ascending UTI
- *Lactobacillus* may prevent vaginal colonisation
- Vaginal administration of *Lactobacillus* induces
  - Persistent colonisation
  - Reduction vaginal coliform counts
  - Reduction of rUTI ?
- Best *Lactobacillus*
  - Produce H_2O_2, adhere to uroepithelial cells, interfere with attachment and growth of *E. coli*, persist in the vagina
- *L. crispatus* does all that (hopefully!!)

Staplaton AE *et al.* CID 2011

L. crispatus intravaginally for prevention of rUTI

Randomized, placebo-controlled Phase 2

- Lactin-V (n=48) or placebo (n=48)
- Intravaginal supository for 5 days plus once/week for 10 weeks.
- Follow-up visit after one week and 10 weeks
- End-points :
  - ✓ rUTI
  - ✓ Levels of *L.crispatus* colonisation (qPCR)

Staplaton AE *et al.* CID 2011

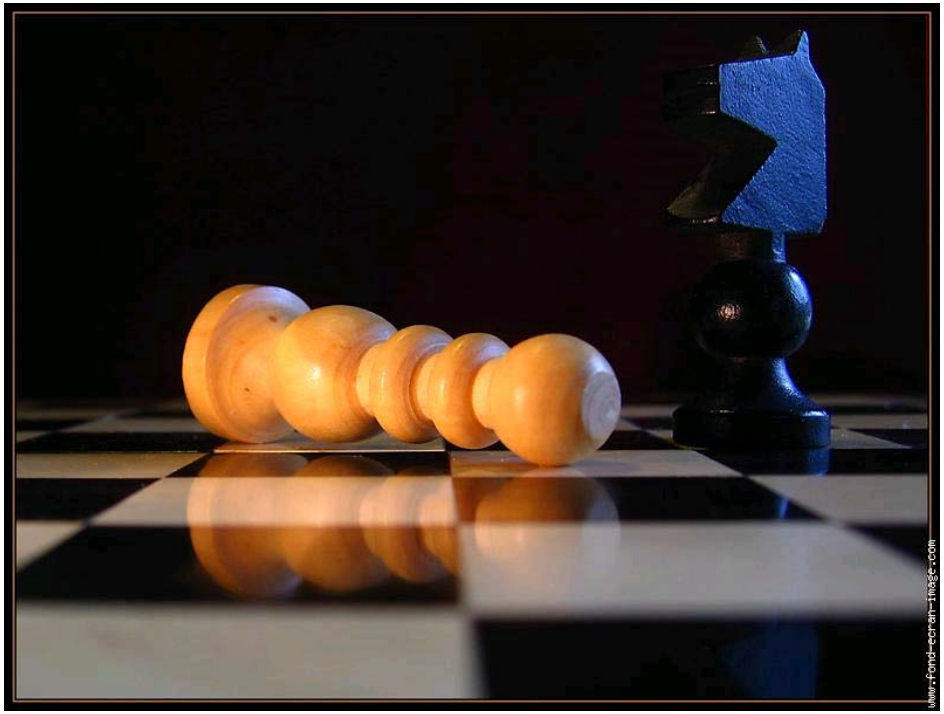
L. crispatus intravaginally for prevention of rUTI

Randomized, placebo-controlled Phase 2

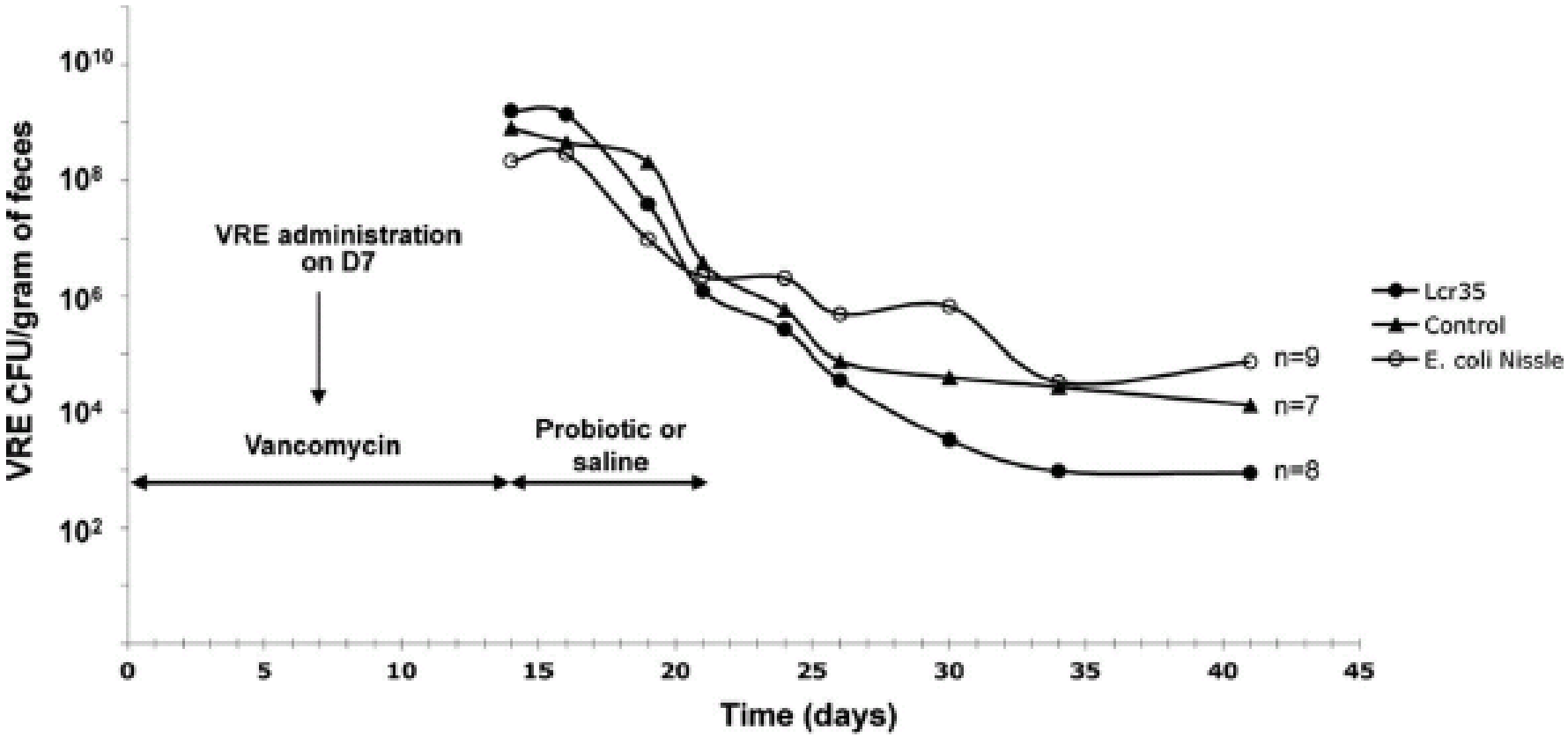
Intervention	No. (%) of participants developing recurrent UTI	Relative risk (95% CI)
Lactin-V ($n = 48$)	7 (15)	.5 (.2–1.2)
Placebo ($n = 48$)	13 (27)	…
Intervention, *L. crispatus* colonization pattern		
Lactin-V, high level ($n = 41$)	2 (5)	.07 (.02–.3)
Lactin-V, low level ($n = 7$)	5 (71)	…
Placebo, high level ($n = 32$)	9 (28)	1.1 (.4–3.1)
Placebo, low level ($n = 16$)	4 (25)	

Staplaton AE *et al.*. CID 2011

VRE colonisation



Effect of probiotic on VRE colonisation in mice.

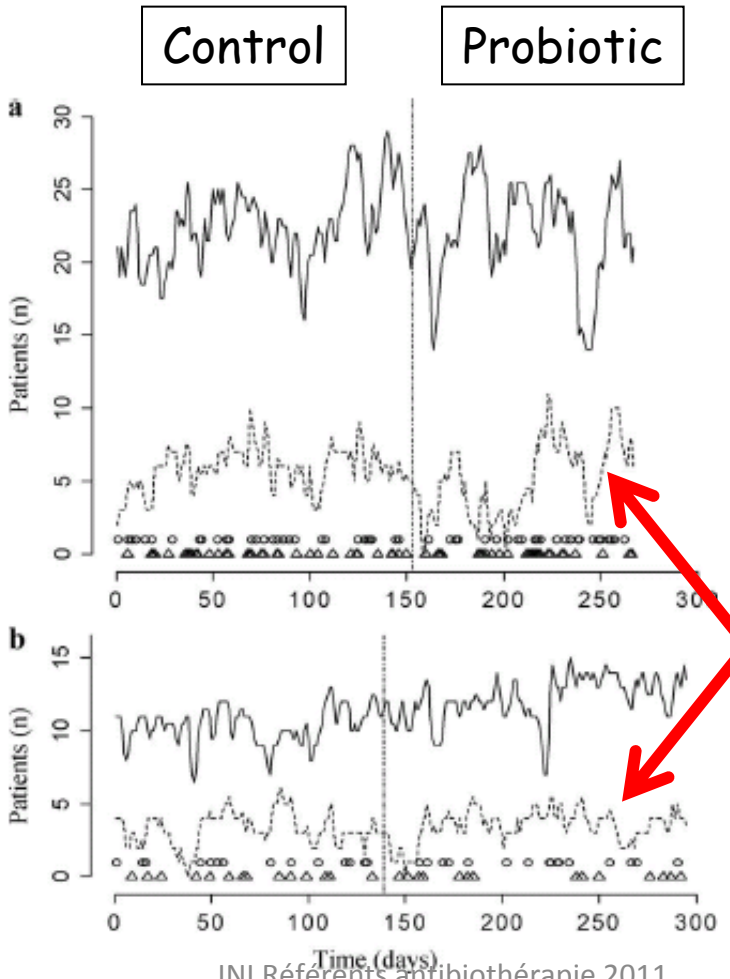


Vidal, M. *et al.* JCM 2010

Effect of probiotic on VRE colonisation in mice.

Gastro nephro

Geriatry



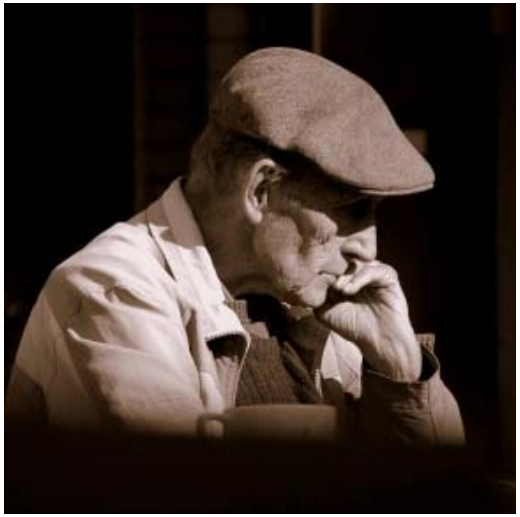
Multispecies probiotic

Bifidus 4, *Lactobacillus* 5, *Enterococcus* 1

VRE colonisation

De Regt MJA, *et al. AAC* 2010

Prevention of VAP



Probiotic prophylaxis of VAP

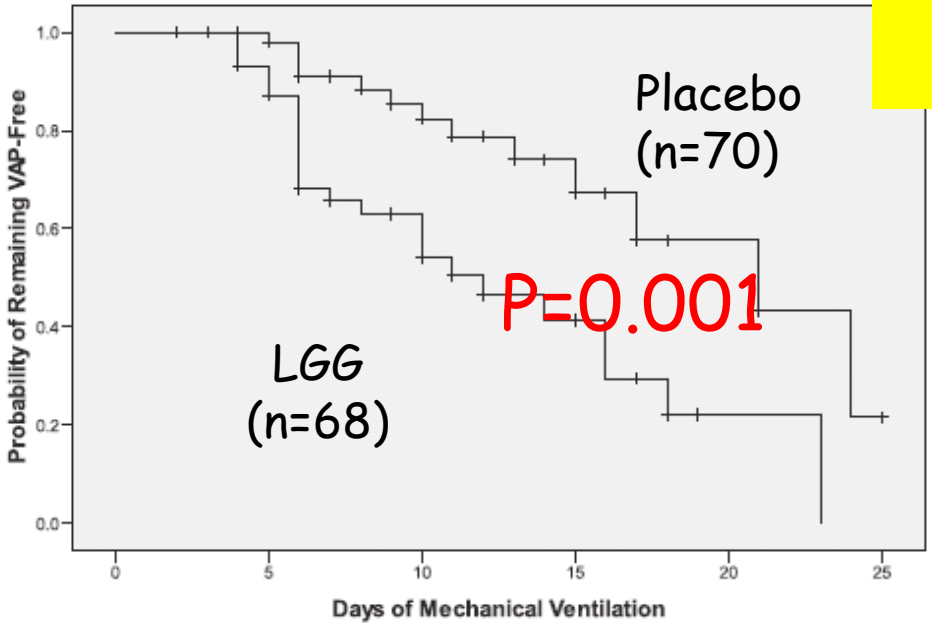
- Adults with ventilation for predicted>72h
- 42 % exclusion for risk of probiotic infection (pregnancy; immunosuppression; prosthetic cardiac valve or vascular graft; cardiac trauma; history of rheumatic fever, endocarditis, or congenital cardiac abnormality; gastroesophageal or intestinal injury or foregut surgery during the current admission; oropharyngeal mucosal injury; and placement of a tracheostomy).
- Lacto *GG* $2X10^9$ twice daily *vs* Placebo
- Microbiologically confirmed VAP on quantitative BAL

Morrow LE *et al.* AJRCCM 2010

LGG for prention of VAP : results

- Significant decreases:
  - ✓CDAD p=0.02
  - ✓Antibioics for VAP p= 0.05
- No difference:
  - ✓Death,
  - ✓Total antibiotics
  - ✓Hosp stay and charges
  - ✓Duration of ventilation

Time to VAP



Morrow LE *et al.* AJRCCM 2010

LGG for prention of

However,

- Other studies not always postives
- 2 Meta-analysis contradictory
- Adverse effects not adequately studied

0.05

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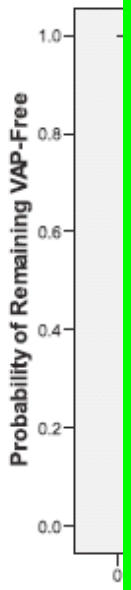

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Predicted severe acute pandreatis

Probiotic prophylaxis in predicted severe acute pancreatitis

- Multicentre randomised, double-blind, placebo-controlled trial,
- acute pancreatitis randomly assigned within 72 h of onset
  - Multispecies probiotic preparation (n=153) *L. acidophilus, L. casei, L. salivarius, L. lactis, B.bifidum, and B.lactis*
  - Placebo (n=145),
  - enterally twice daily for 28 days.
- The primary endpoint was the composite of infection 90-day follow-up. ATT

Besselink, GH *et al.* Lancet 2008; 371: 651–59

	Probiotics (N=152)	Placebo (N=144)	p value
Primary endpoint			
Any infectious complication*	46 (30%)	41 (28%)	0·80
Infected necrosis	21 (14%)	14 (10%)	0·29
Bacteraemia	33 (22%)	22 (15%)	0·18
Pneumonia	24 (16%)	16 (11%)	0·31
Urosepsis	1 (0·7%)	2 (1%)	0·61
Infected ascites	4 (3%)	0 (0%)	0·12
Secondary endpoint			
Use of antibiotics, any indication	75 (49%)	76 (53%)	0·56
Percutaneous drainage	14 (9%)	8 (6%)	0·23
Surgical intervention, any indication	28 (18%)	14 (10%)	0·05
Necrosectomy	24 (16%)	14 (10%)	0·16
Intensive care admission	47 (31%)	34 (24%)	0·19
Intensive care stay (days)	6·6 (17·1)	3·0 (9·3)	0·08
Hospital stay (days)	28·9 (41·5)	23·5 (25·9)	0·98
Organ failure during admission, any onset†‡	41 (27%)	23 (16%)	0·02
Multiorgan failure during admission, any onset‡	33 (22%)	15 (10%)	0·01
Organ failure, onset after randomisation†§	21 (14%)	16 (11%)	0·60
Multiorgan failure, onset after randomisation§	18 (12%)	11 (8%)	0·25
Nausea	20 (13%)	23 (16%)	0·51
Abdominal fullness	36 (24%)	43 (30%)	0·24
Diarrhoea	25 (16%)	28 (19%)	0·55
Bowel ischaemia	9 (6%)	0 (0%)	0·004
Mortality	24 (16%)	9 (6%)	0·01

Data are mean (SD) or n (%). *Patients with one or more infectious complication. †Patients with multiorgan failure are included in the organ failure group. ‡Patients with organ failure present at any time during admission, irrespective of the date of onset of organ failure, are included. §Patients in whom organ failure developed (for the first time) after the day of randomisation are included. Patients in whom organ failure (in any organ) started before the day of randomisation or on the day of randomisation are not included.

Table 2: Endpoints

Nothing on primary end-points!

Highly singificant overmortality!

Besselink, GH *et al.* Lancet 2008

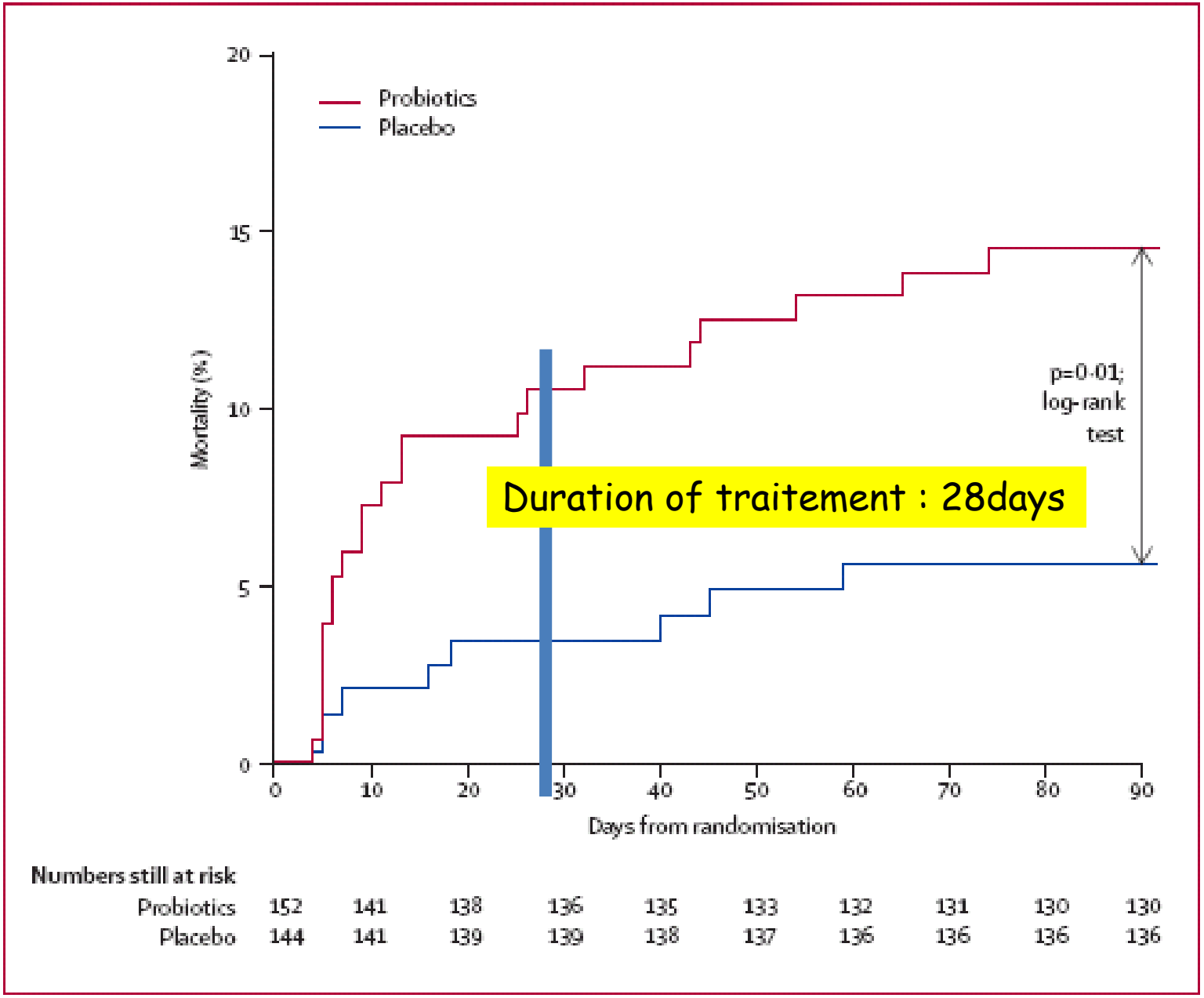

Figure 2: Kaplan-Meier time-to-event analysis for mortality in the first 90 days after randomisation
A follow-up of longer than 90 days was obtained in 266 (90%) patients. Three deaths occurred after 90 days: two in the probiotics group (day 112 and 125) and one in the placebo group (day 140).

Besselink, GH *et al.* Lancet 2008

Positions, regulators and so forth

Regulatory Oversight and Safety of Probiotic Use

- ✓Before use of a probiotic is considered for hospitalized patients, careful assessement of risk versus benefit must be made.
- ✓To ensure patients safety, probiotics should be properly handled during administration.

Venugopalan V *et al.* **EID** 2010

Scientific Opinion EFSA
L. rhamnosus GG and pathogenic GI microorganisms

- Claim "maintenance of defence against pathogenic GI microorganisms".
- Strain sufficiently characterised.
- 45 human and 41 non-human studies.
- "cause and effect relationship has not been established…."

EFSA Journal 2011;9(6):2167

Probiotics in pediatrics
Guidance from American academy of pediatrics

- Modestly effective :
  - Acute viral gastroenteritis, AAD in healthy children
- Some evidence
  - NEC (between 1000-1500g) More studies needed
- Encouraging need of confirmation
  - H. pylori, IBS, CUC, Infantile colic, Childhood atopy
- No effectiveness
  - Cancer, Crohndiseases
- Safety concerns
  - Immunocompromised, debilitated, ill with catheters

Thomas DW *et al.* Pediatrics 2010

Au 8 Juin 2011: Des frémissements mais beaucoup d'incertitudes…