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Prophylactic probiotics for the prevention of cancer therapy-induced diarrhea: a meta-analysis

Dr Hannah Wardill, Dr Ysabella Van Sebille, Dr Matt Ciorba and A/Prof Joanne Bowen

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The University of Adelaide (Adelaide Medical School)
The University of Groningen (University Medical Centre Groningen / Beatrix Children's Hospital)


MICRO
BIOME

Evolution of the microbiome in mucositis research

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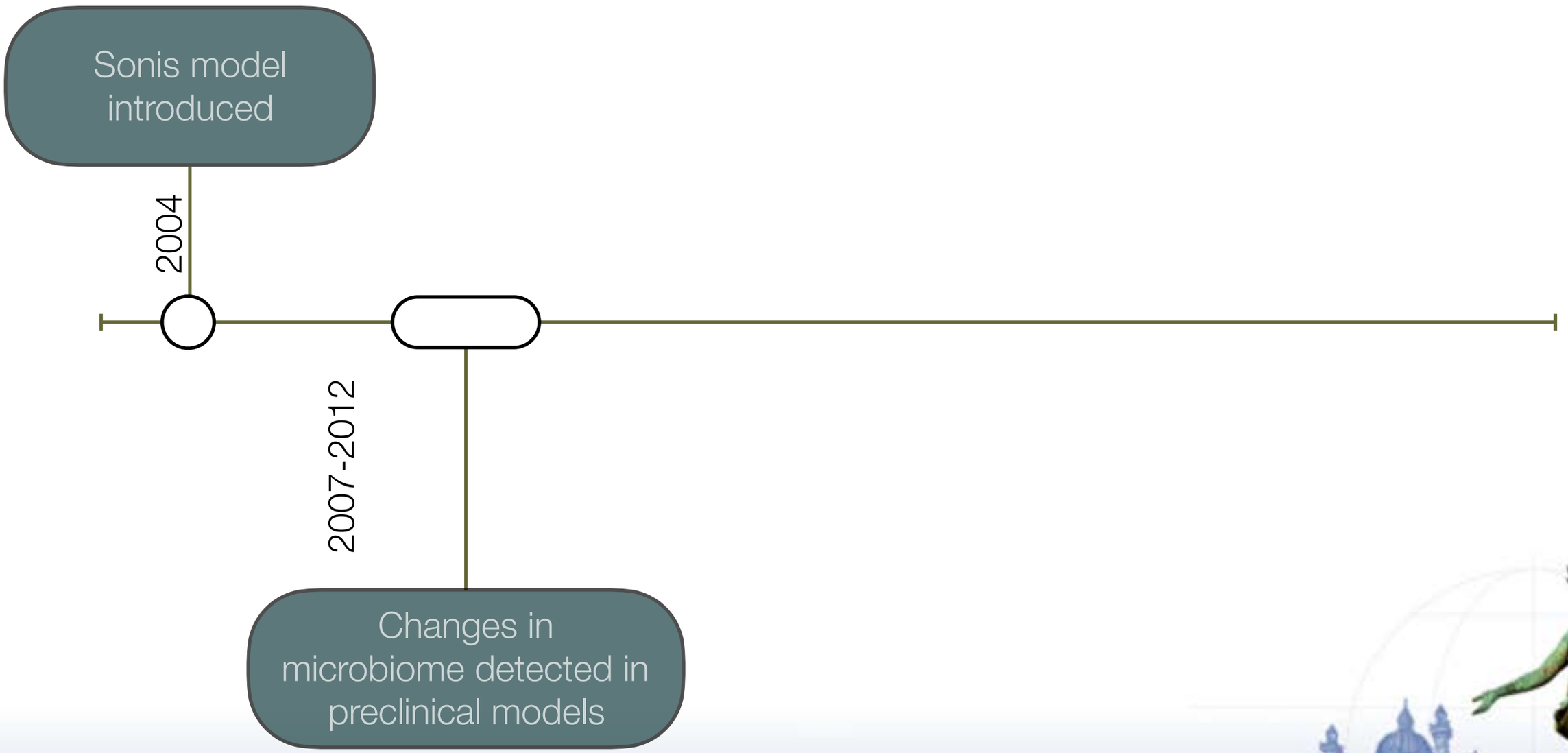

Stringer et al., Von Bultzinglowen et al., Lin et al., and Johnson et al.

Evolution of the microbiome in mucositis research

Sonis model introduced

2004

2007-2012

16S rRNA sequencing introduced

Metagenomic approaches more readily utilised

Changes in microbiome detected in preclinical models

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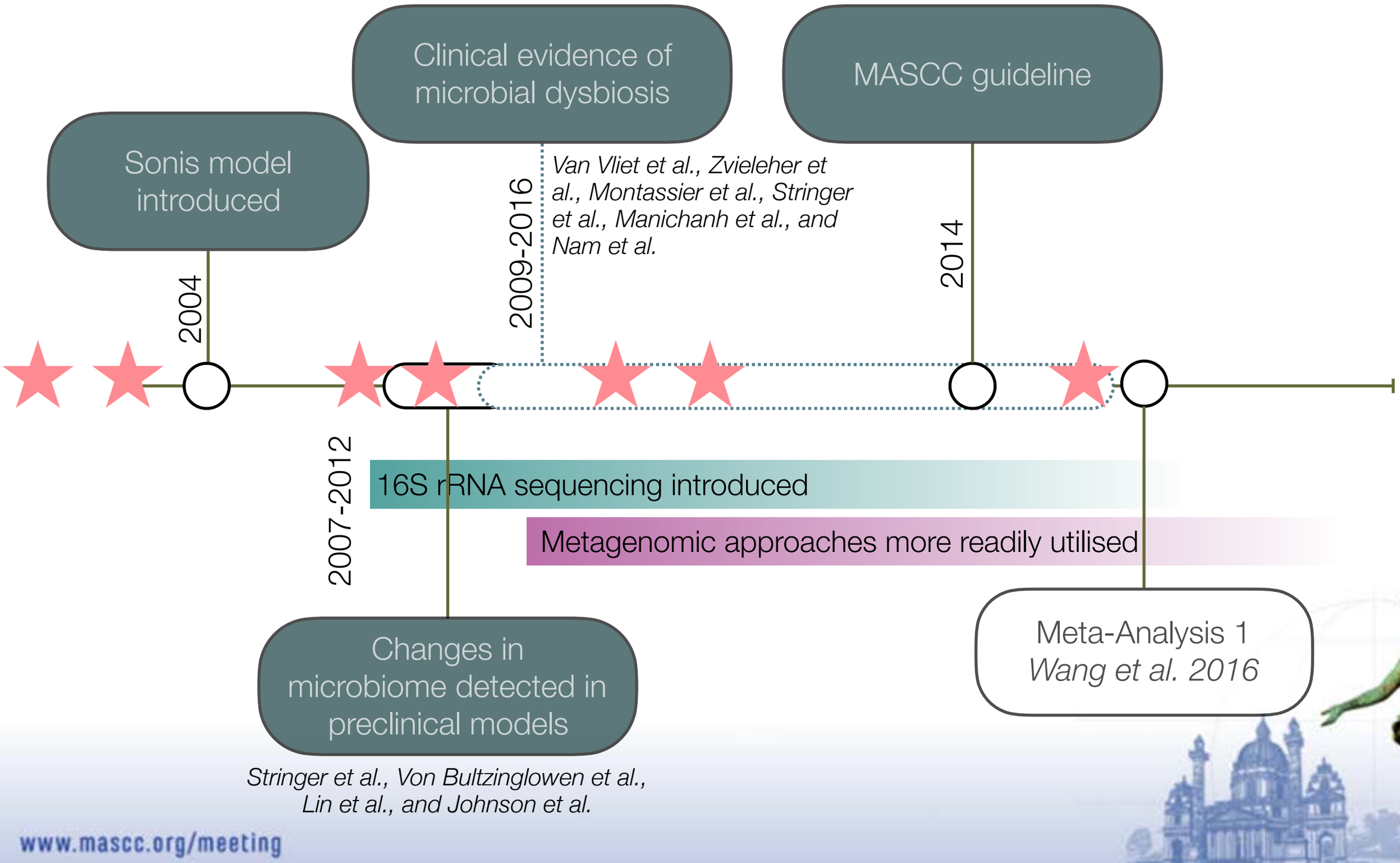
Current MASCC guidelines

"The panel ***suggests*** that probiotics containing *Lactobacillus* species be used to ***prevent*** diarrhea in patients receiving chemotherapy and/or radiation therapy for a ***pelvic*** malignancy" *Lalla et al., 2014*

Evolution of the microbiome in mucositis research



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Meta-Analysis 2
Lui et al., 2017

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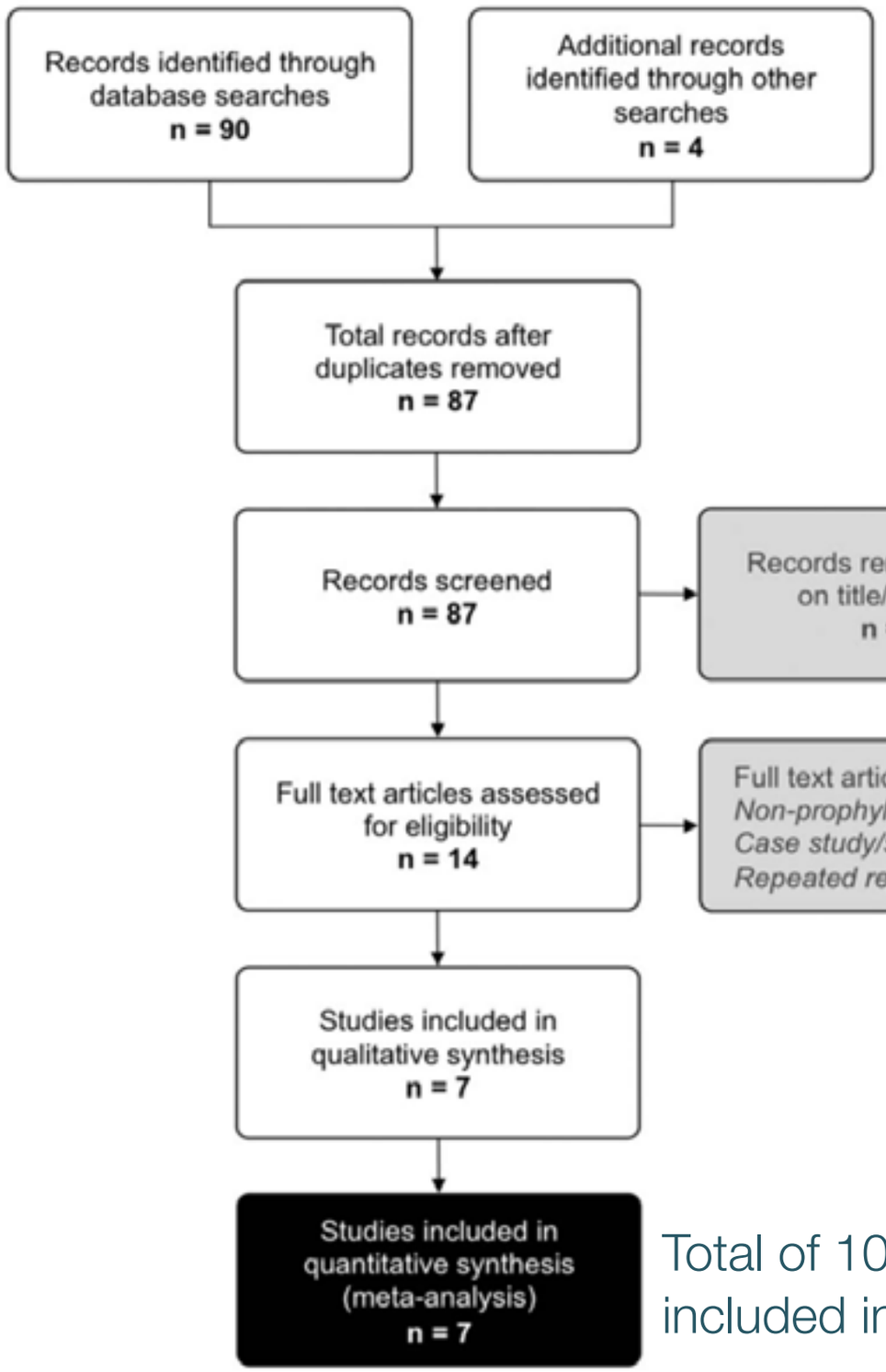
Meta-Analysis 1
Wang et al. 2016

Meta-analysis protocol



June 1 2000 - June 1 2017

Total of 1090 patients included in meta-analysis

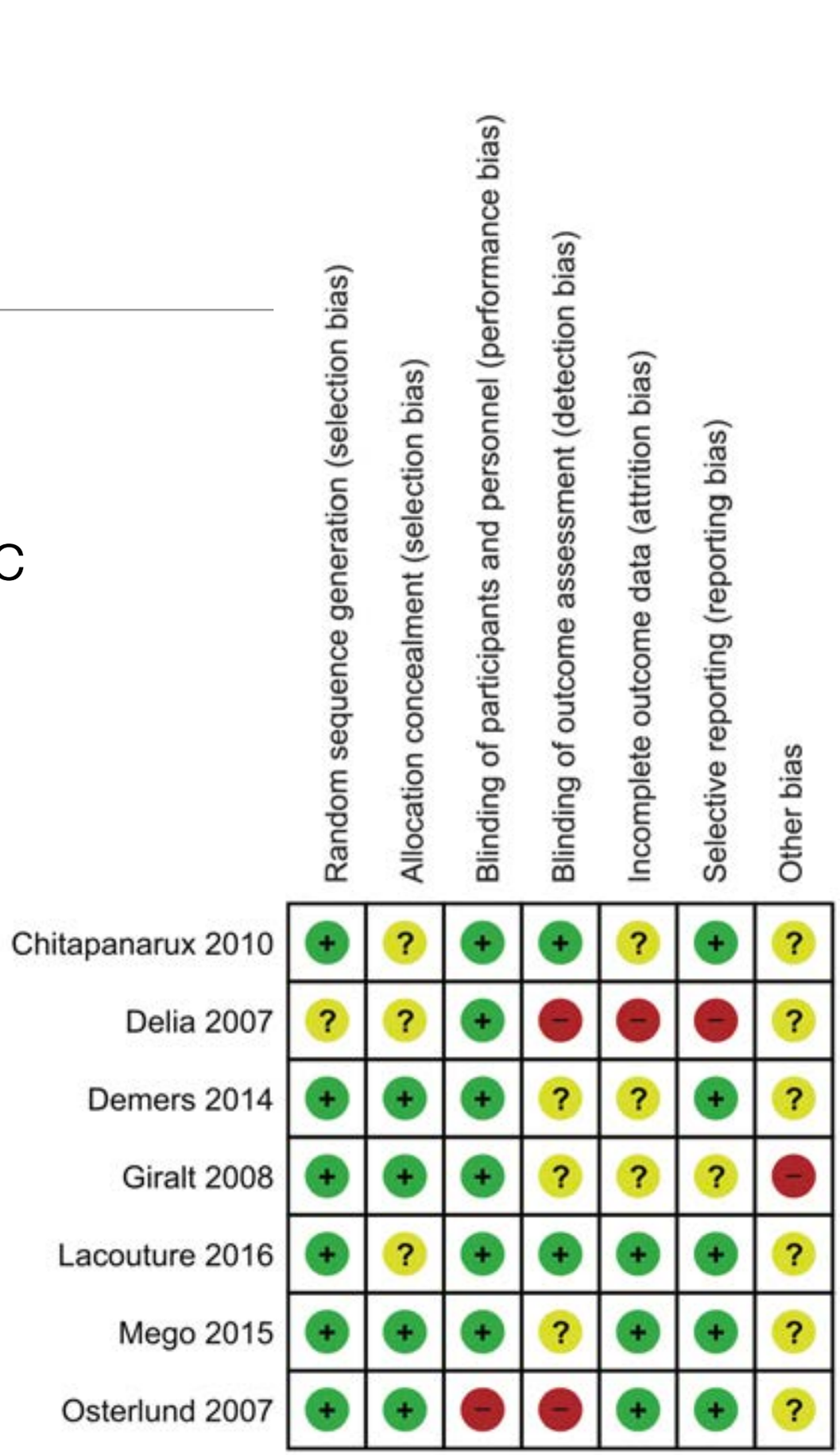
Study characteristics

Table 1: Characteristics of studies included for meta-analysis.

Study	Patients (N)	Diagnoses	Treatment(s)	Probiotic Type/Source/Schedule
Chitapanarux 2010	N=32 (pro) N=31 (cont)	Cervical	Pelvic radiotherapy (200 cGy /fraction, 5 fraction/ wk) and wkly cisplatin (40 mg/m^2, 6 wk)	Lactobacilli and bifidobacteria (4x10^9 CFU); Laboratio Farmaceutico SIT (Mede, Italy); Probiotic provided 1 week before treatment and for duration of treatment.
Delia 2007	N=243 (pro) N=239 (cont)	Sigmoid, rectal and cervical	Postoperative radiotherapy (60-70 Gy)	Lactobacilli, bifidobacteria and streptococcus (1.35 x 10^{12} CFU);VSL Pharmaceuticals (Fort Lauderdale MD, USA); Duration of treatment (daily)
Demers 2014	N=140 (pro) N=86 (cont)	Gyn, rectal, prostate	Radiotherapy (40 Gy) +/- chemotherapy	Lactobacilli and bifidobacteria (LD: 2.6 x 10^9 CFU, or HD: 3 x 10^9 CFU); Bifilact, virage Santé, Québec City, Canada; Duration of treatment
Giralt 2008	N=44 (pro) N=41 (cont)	Endometrial adeno, advanced cervical squamous cell	Post-operative radiotherapy (45-50.4 Gy), concomitant weekly cisplatin (40 mg/m^2, only for patients with cervical	Streptococcus thermophillus, Lactobacillus delbrueckii subsp. bulgaricus + 96 ml of fermented liquid yoghurt (3x daily) containing 10^8 CFU/g L.casei DN114001; Source not reported.; Probiotic provided 1 week before tx and for duration of tx.
Lacatoure 2016	N=58 (pro) N=59 (cont)	Advanced NSCLC	Dacomitinib, (45 mg, daily, continuous)	VSL#3 (4 capsules daily, for duration of study); Source not reported.
Mego 2015	N=23 (pro) N=23 (cont)	Colorectal	Irinotecan, 5-FU, capecitabine, bevacizumab, cetuximab	Colon dophilus; Harmonion International Inc. Mirabel, Canada; 10 x10^9 CFU/day for 12 weeks (3 x daily)
Osterlund 2007	N=52 (pro) N=98 (cont)	Colorectal	5-FU (370-425 mg/m^2) for 24 wk with concomitant	Lactobacillus rhamnosus (2x daily; 1-2 x 10^{10} CFU); Gefilus Valio Ltd, Helsinki Finland; Duration of treatment.

Results: overall risk of bias

- Overall studies were fairly robust
- Delia et al., was most problematic (multiple publications)
- Inconsistent outcome data



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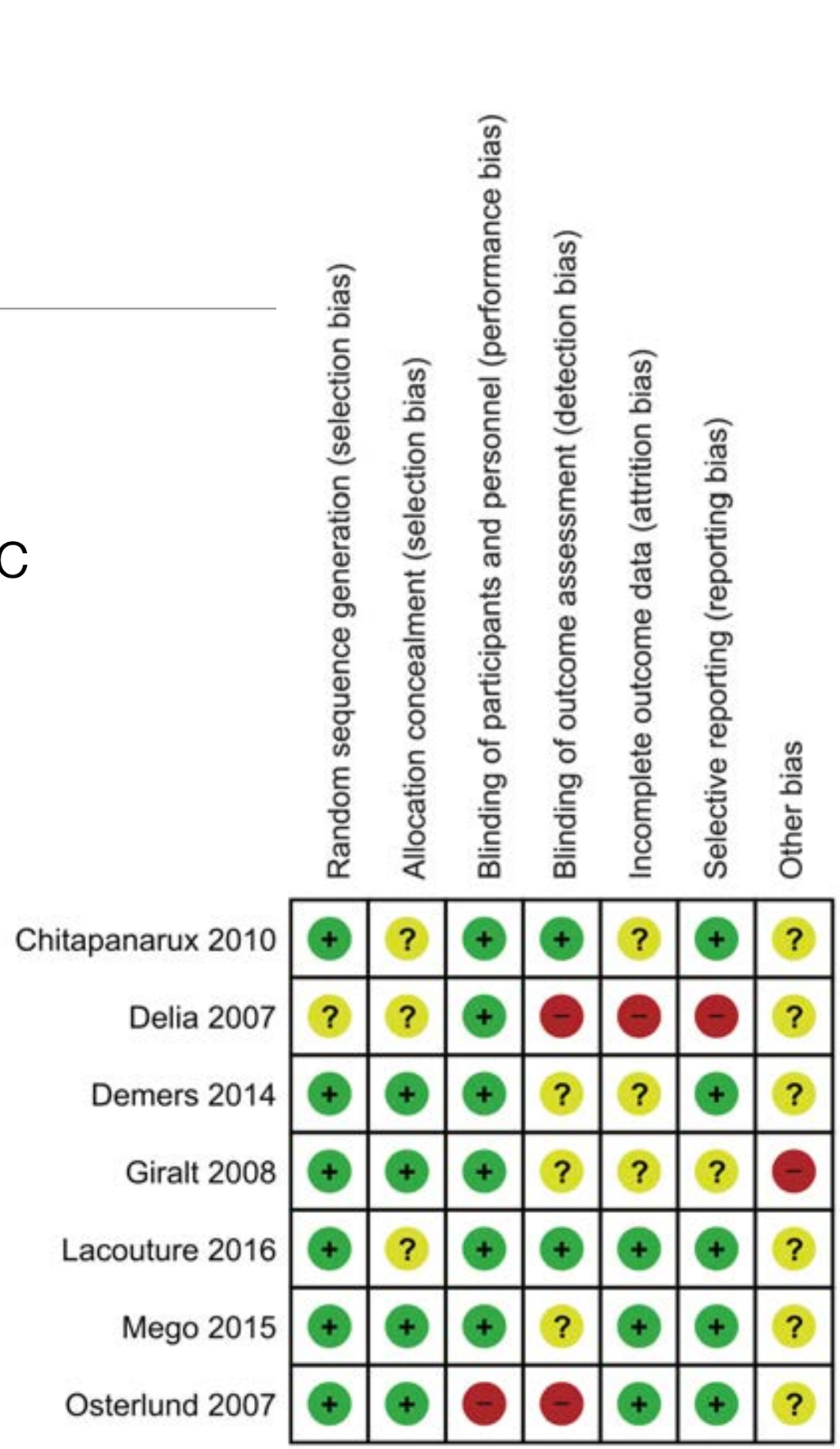
1. Overall diarrhea severity



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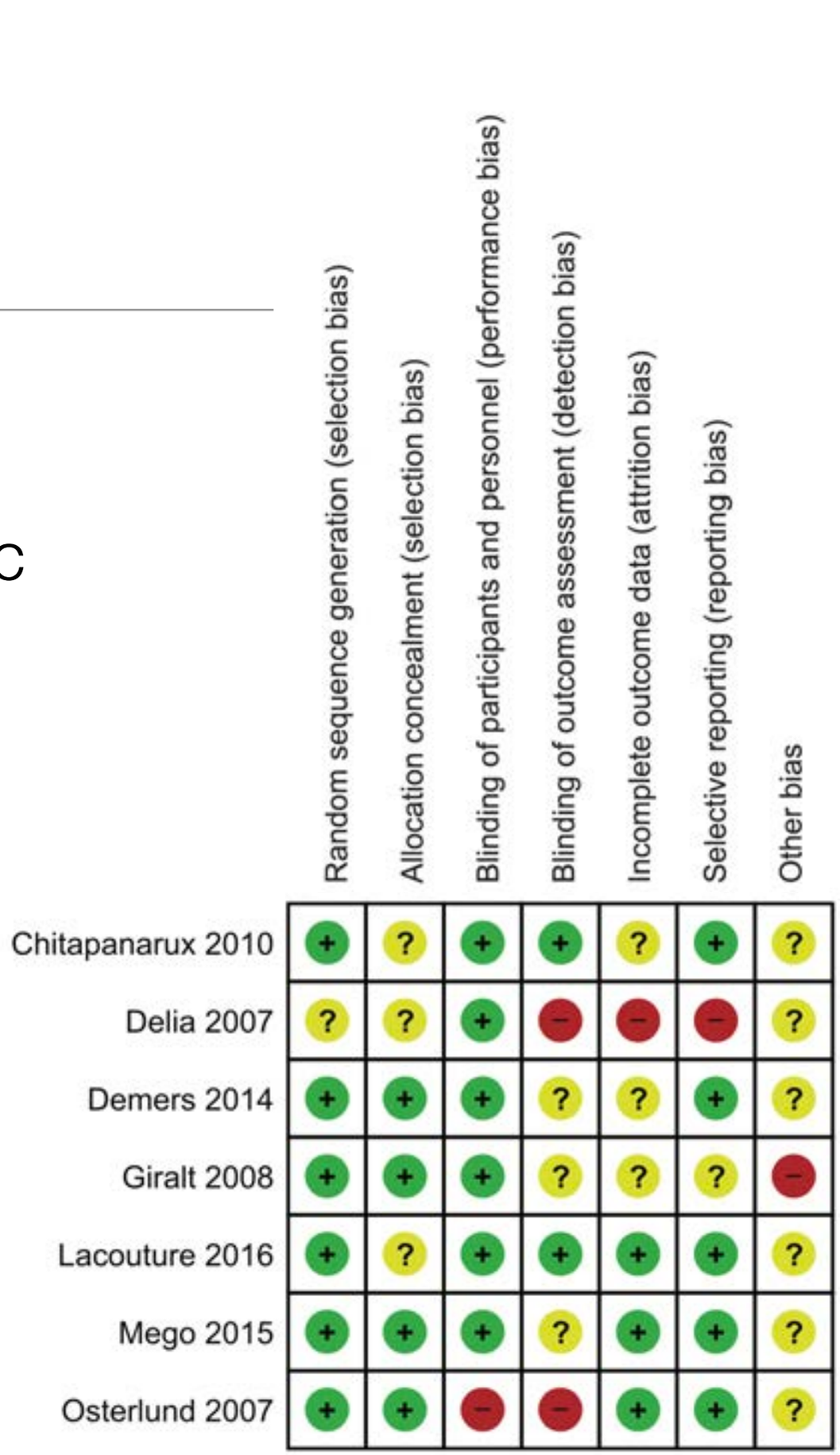
1. Overall diarrhea severity
2. Incidence of severe diarrhea



Results: overall risk of bias

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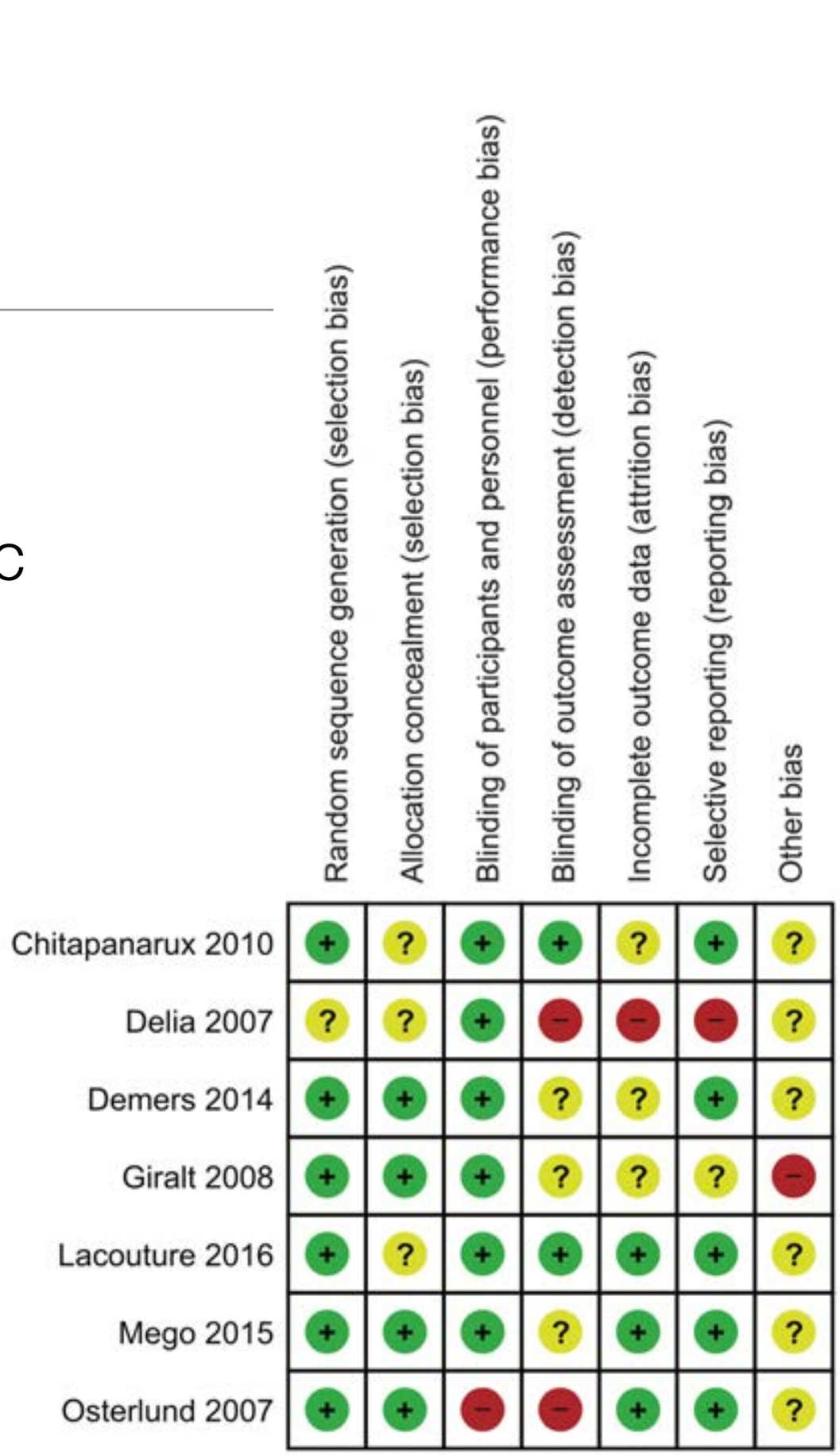
1. **Overall diarrhea severity**
2. **Incidence of severe diarrhea**
3. **Use of rescue medication**

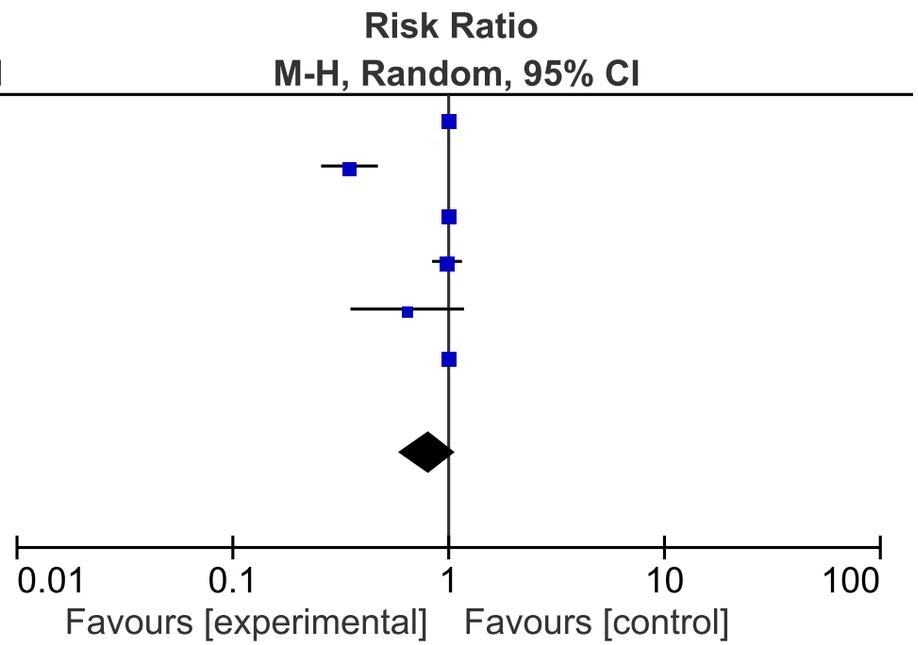


Results: diarrhoea incidence

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Chitapanarux 2010	32	32	31	31	18.6%	1.00 [0.94, 1.06]
Delia 2007	42	243	119	239	15.7%	0.35 [0.26, 0.47]
Demers 2014	140	140	86	86	18.7%	1.00 [0.98, 1.02]
Lacouture 2016	49	59	49	58	17.8%	0.98 [0.84, 1.15]
Mego 2015	9	23	14	23	10.6%	0.64 [0.35, 1.18]
Osterlund 2007	97	97	51	51	18.7%	1.00 [0.97, 1.03]
Total (95% CI)		**594**		**488**	**100.0%**	**0.81 [0.60, 1.09]**
Total events	369		350			

Heterogeneity: Tau² = 0.12; Chi² = 991.21, df = 5 (P < 0.00001); I² = 99%

Test for overall effect: Z = 1.41 (P = 0.16)



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Delia 2007	8	243	69	239	17.3%	0.11 [0.06, 0.23]
Demers 2014	46	140	26	86	19.2%	1.09 [0.73, 1.62]
Giralt 2008	20	44	15	41	18.5%	1.24 [0.74, 2.08]
Lacouture 2016	9	59	8	58	16.0%	1.11 [0.46, 2.67]
Mego 2015	0	23	4	23	5.3%	0.11 [0.01, 1.95]
Osterlund 2007	21	97	19	51	18.5%	0.58 [0.35, 0.98]
Total (95% CI)		**638**		**529**	**100.0%**	**0.54 [0.25, 1.16]**
Total events	104		144			

Heterogeneity: Tau² = 0.77; Chi² = 44.33, df = 6 (P < 0.00001); I² = 86%

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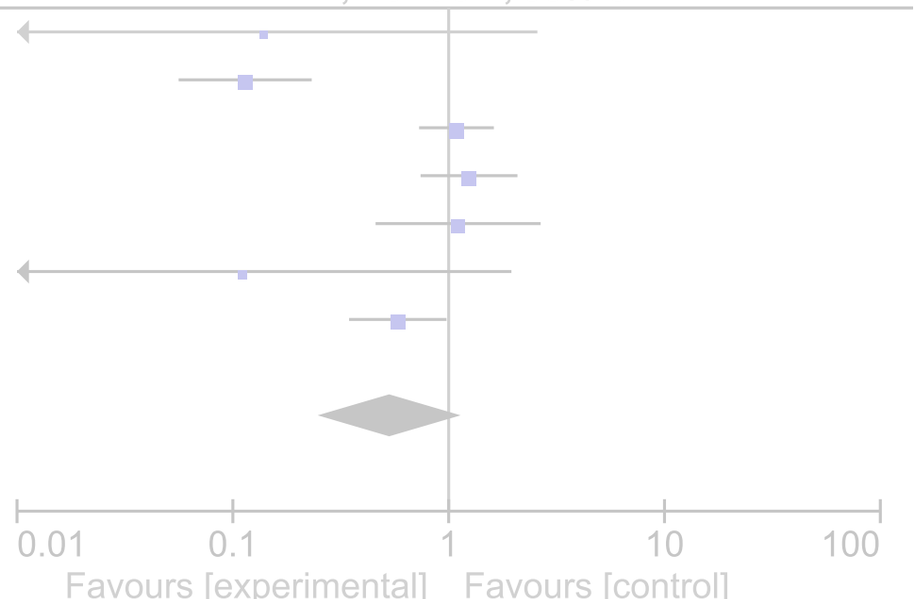

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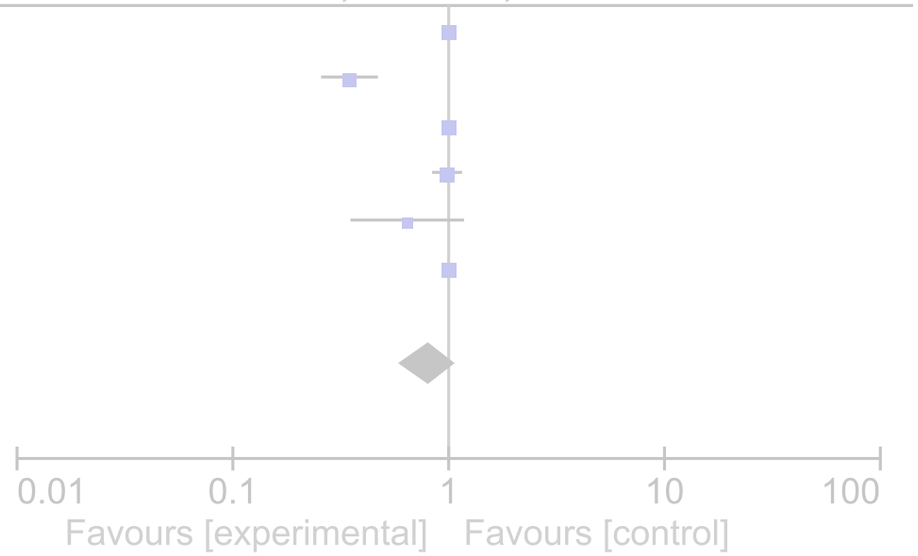

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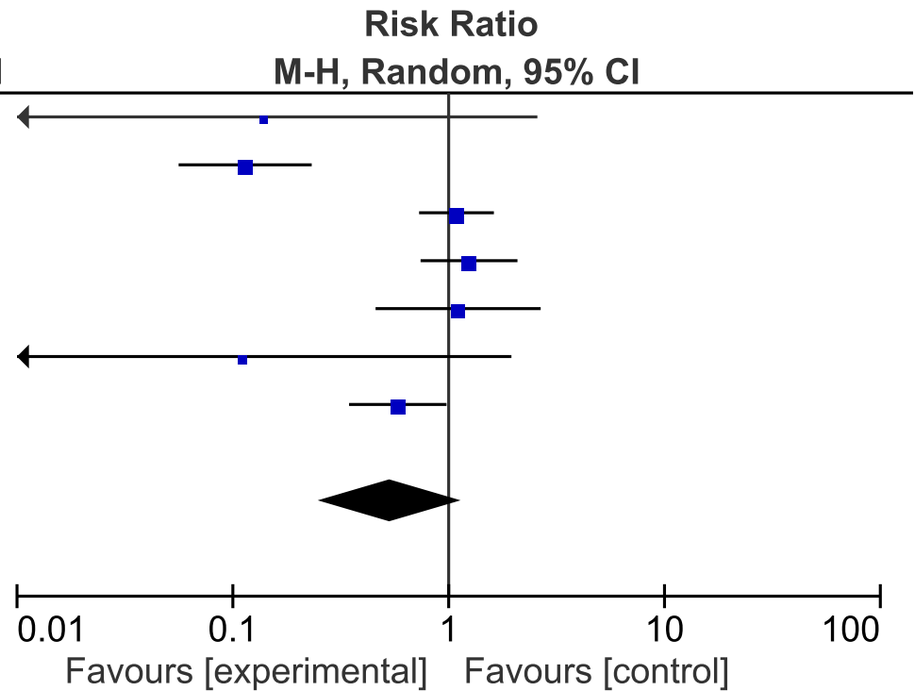
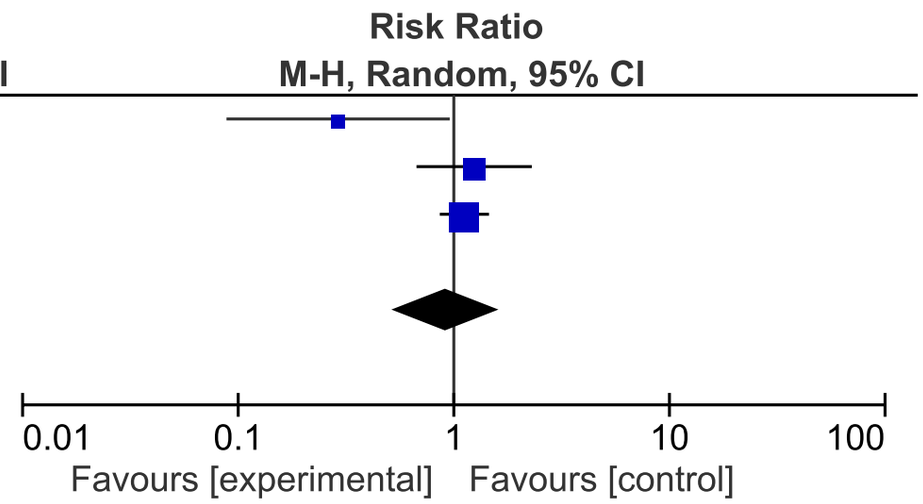


Results: use of rescue medication

Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Chitapanarux 2010	3	32	10	31	16.3%	0.29 [0.09, 0.96]
Giralt 2008	16	44	12	41	33.8%	1.24 [0.67, 2.30]
Lacouture 2016	41	59	36	58	49.9%	1.12 [0.86, 1.46]
Total (95% CI)		**135**		**130**	**100.0%**	**0.93 [0.53, 1.65]**
Total events	60		58			

Heterogeneity: Tau² = 0.15; Chi² = 5.29, df = 2 (P = 0.07); I² = 62%
Test for overall effect: Z = 0.24 (P = 0.81)



What does it mean for the future of probiotics?

- Most **comprehensive** meta-analysis (including all forms of cancer treatment, excl. surgery)
- **No overall benefit** of probiotics for the prevention of "cancer therapy" induced diarrhea
  - Negative results reflect breadth of studies included (e.g. Lacouture et al., 2016)
  - Data support continued use in patients with pelvic malignancy

Obstacles encountered and future directions

Obstacles

- Variation in endpoint analyses (e.g. mucositis/diarrhea assessment, self-reported vs clinician-reported)
- Lack of objective biomarker that is uniformly applicable

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Recommendations

- **Take a step back …** characterise ‘ideal’ microbial composition (likely to be different for each treatment type)
  - These studies should involve an experienced microbiologist or bioinformatics expert
  - Pair specific forms of toxicity with unique microbial phenotype
- **Intelligent study design …** uniform grading systems, inclusion of gastroenterologist or ‘onco-gastroenterologist’

Acknowledgements

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CANCER TREATMENT TOXICITIES GROUP

Integrating the pathogenesis, prediction and prevention of cancer-related side effects

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REVIEW

Prophylactic probiotics for cancer therapy-induced diarrhoea: a meta-analysis

Hannah R. Wardill[a,b], *Ysabella Z.A. Van Sebille*[c], *Matthew A. Ciorba*[d], *and Joanne M. Bowen*[a]

Purpose of review
Strong preclinical data support prophylactic probiotics as an effective preventive strategy for diarrhoea secondary to anticancer therapies. To determine the composite evidence that this approach translates to the clinic, we performed a meta-analysis of randomized controlled trials (RCTs) of prophylactic probiotics for the prevention of cancer therapy induced diarrhoea.

Recent findings
A three-step search strategy was used to identify relevant studies (1 June 2000–1 June 2017) investigating probiotic intervention for diarrhoea secondary to any cancer therapy (cytotoxic, targeted and immunotherapies). RCTs across PubMed, Embase, CINAHL and CENTRAL were assessed for eligibility and assessed using RevMan 5.3 (The Cochrane Collaboration). Seven trials with a total of 1091 patients were included in this meta-analysis. Compared with placebo, prophylactic probiotics did not prevent or reduce the overall incidence of diarrhoea or severe CTCAE Grade at least 3 diarrhoea [relative risk (RR) = 0.81, 95% confidence interval (95% CI) = 0.60–1.09, $Z = 1.41$, $P = 0.16$; RR = 0.54, 95% CI = 0.25–1.16, $Z = 1.58$, $P = 0.11$], nor did it influence the use of rescue medication (RR = 0.93, 95% CI = 0.53–1.65, $Z = 0.24$, $P = 0.81$).

Summary
Current evidence does not support widespread implementation of probiotics for diarrhoea secondary to