

# A SYSTEMATIC REVIEW ON THE EFFECTIVENESS AND SAFETY OF PROBIOTICS FOR THE TREATMENT OF ACUTE DIARRHEA IN CHILDREN

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## BACKGROUND

Although probiotic strains are closely related, they can have different clinical effects. A systematic review was conducted to evaluate the effectiveness and safety of probiotic use to treat acute diarrhea in hospitalized children.

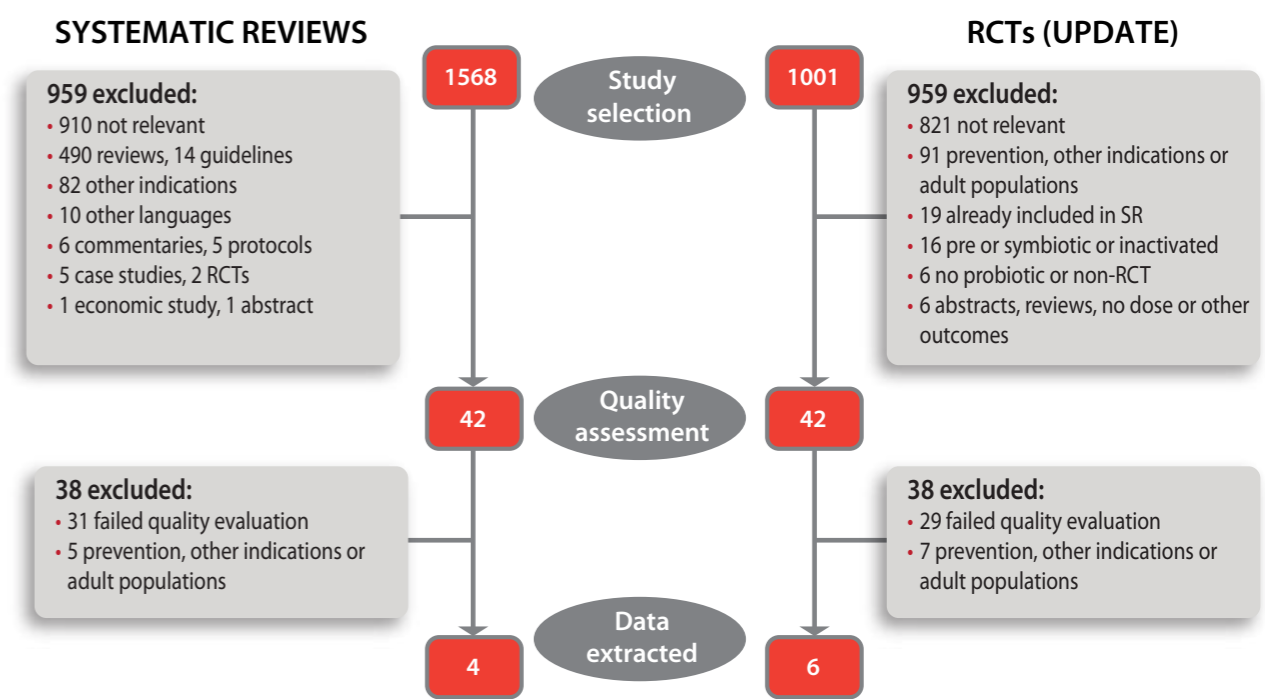
**Inclusion criteria:** Probiotics defined at the genus and species level, with a specified dose, and administered through the digestive tract. Data on duration or frequency of diarrhea lasting three or more days, and proven sepsis (caused by the same microorganisms than those of the probiotic therapy confirmed by a molecular test).

**Exclusion criteria:** *In vitro* or animal studies, publications in another language than French or English, studies that failed quality evaluation.

Article selection, quality assessment and data extraction were performed by two independent reviewers using standardized forms (UETMIS, 2007). Discrepancies were resolved by including a third reviewer to reach a consensus.

Results were analyzed by probiotic type. Synthesis review was shared with a medical interdisciplinary group composed of gastroenterologist, pediatricians, nurse, infectiologist, pharmacist, nutritionist, and managers.

Figure 1. Study selection process for effectiveness evaluation



## METHODS

Systematic reviews (SRs) and randomized controlled trials (RCTs) were searched in PubMed, Embase, Cochrane Central Register of Controlled Trials, and grey literature databases (January 1995 to September 2009). Prospective studies, case reports, and case series were also retrieved to evaluate safety. Update of the last SR was performed.

## FINDINGS

- Four SRs (Szajewska, 2001; 2007a; 2007b; Allen, 2003) including 26 RCTs.
- Update: 6 RCTs (Sarker, 2005; Szymanski, 2006; Canani, 2007; Misra, 2007; Basu, 2007; 2009).
- Table 1 displays the main characteristics of the RCT populations and studies with criteria to define case and cessation diarrhea.
- Table 2 displays the mean differences in the diarrhea duration observed in RCTs.

Table 1. Characteristics of RCTs according to study population, criteria for diarrhea and probiotic type

Probiotics (n RCTs)	Age in months (n RCTs)				Inclusion of inpatients only (n RCTs)	Inclusion of Malnourished infants <sup>a</sup> (n RCTs)		Criteria for diarrhea <sup>b</sup> (n RCTs)	
	0-36	0-48	0>48	NR		Yes	NR	Case	Cessation
LGG (17)	13	2	-	2	13 <sup>c</sup>	5	6	15	6 <sup>d</sup>
<i>S. boulardii</i> (5)	2	-	3	-	3	2	2	2	1
Others (11) <sup>e</sup>	6	2	-	3	8	5	5	6	6

LGG: *Lactobacillus rhamnosus* or *casei*; *S. Saccharomyces*  
 NR: not reported or not available  
<sup>a</sup> Other language in one RCT  
<sup>b</sup> Presence of two criteria: a specified number of stools and duration  
<sup>c</sup> 86% inpatients in one RCT  
<sup>d</sup> Not evaluated in one RCT  
<sup>e</sup> Two unpublished RCTs

Table 2. Mean differences in diarrhea duration between probiotic (P) and control (C) groups in RCTs

Probiotic	RCT (n)	Direction of effect	Mean difference, range, P-C (hours)	p value	
<b>LGG</b>	Any etiology	11	↓	-72 to -14	s.
		2	↓	-12 to -7	n.s.
		3	↑	1 to 8	n.s.
Rotavirus	6	↓	-77 to -19	s.	
<b><i>S. boulardii</i></b>	Any etiology	4	↓	-35 to -22	s.
		1	↓	-5	n.s.
		Rotavirus	-	-	-
<b>Other species</b>	Any etiology	3	↓	-51 to -24	s.
		5	↓	-40 to -2	n.s.
		2	↑	1 to 2	n.s.
Rotavirus	1	↓	-24	s.	
	1	↓	-1	n.s.	

LGG: *Lactobacillus rhamnosus* or *casei*; *S. Saccharomyces*  
 s.: statistically significant, p<0.05; n.s.: not statistically significant, p>0.05

## Effectiveness

- According to Allen et al. (2003), Szajewska et al. (2007a), Canani et al. (2007), and Basu et al. (2009), **LGG** reduced the mean duration of diarrhea. In three RCTs, risk of diarrhea lasting three or more days was significantly lower among probiotic group (data not shown). However, heterogeneity regarding probiotic dose and duration, definitions of diarrhea and cessation of diarrhea, as well as patient characteristics was observed (table 1). Mean duration of diarrhea caused by rotavirus were also reduced in 6 RCTs (table 1).
- According to Szajewska et al. (2007b), ***S. boulardii*** may reduce mean duration of diarrhea and risk of diarrhea lasting three or more days. However, definition of diarrhea was incomplete in 3/6 studies while for cessation of diarrhea it was not defined in 4/6 studies. Population heterogeneity was also noticed (table 1).
- For **other probiotics**, few studies were performed on similar type and results were inconsistent for mean duration of diarrhea (table 1) and frequency of diarrhea (data not shown).

## Safety

- Probiotics were described as safe in SRs. Few adverse events ("complaint of meteorism" (1), "constipation" (1) and "myoclonic jerking of the limbs" (1)) were reported in RCTs.
- Cases of confirmed sepsis associated with **LGG** and ***S. boulardii*** were observed among vulnerable patients in other studies than SRs and RCTs (table 3).

Table 3. Case reports of confirmed sepsis associated with probiotics in children

Probiotic	Total cases	CVC	Antibiotics <sup>a</sup>	Prematurity	Immunodeficiency
LGG	4	4	2 <sup>b</sup>	2	2
<i>S. boulardii</i>	4	4	4	-	1

CVC: central venous catheter; LGG: *Lactobacillus rhamnosus* or *casei*; *S. Saccharomyces*  
<sup>a</sup> Antibiotics administered before sepsis  
<sup>b</sup> Not reported in two RCTs

## CONCLUSION

Scientific evidence regarding the effectiveness of probiotics to treat acute diarrhea in children is weak to moderate for **LGG** whereas evidence for ***S. boulardii*** is weak. Evidence on the effectiveness of other types of probiotic is undetermined. Nonetheless, further researches are needed to determine dose and treatment duration before a widespread use in healthcare facilities. Probiotic use for treatment of diarrhea in children is usually safe. However, sepsis may occur in patients with underlying conditions, such as immunodeficiency, prematurity or presence of a central venous catheter.

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