The probiotic *Bacillus clausii* in the prevention of antibiotic-associated diarrhoea in children: A pooled analysis of controlled clinical trials

Manuel Plomer [1], Marcos Perez III [1], Barbara Arnotfalvy [2], Darinka Vargas [3], Hai Yen Lam [4], Maria Chiara Uboldi [5]
CHC Medical Affairs, [1] Frankfurt, Germany; [2] Budapest, Hungary; [3] Panama City, Panama; [4] Ho Chi Minh City, Vietnam; [5] Milan, Italy

INTRODUCTION

- *Bacillus clausii (B. clausii)* strains O/C, SIN, N/R and T are used for the prevention of antibiotic-associated diarrhoea (AAD).
- A randomised controlled clinical trial in **adults** showed the incidence of diarrhoea was lower with antibiotics plus *B. clausii* compared with antibiotics plus placebo[1] (9.3% vs 30.8%).
- AAD is common in **children** prescribed antibiotics, but the efficacy of B. clausii is preventing diarrhoea in this population is not know.

OBJECTIVE

To pool clinical evidence for a potential role of *B. clausii* in preventing AAD in children.

METHODS

Literature review (no date/database restrictions)

Search terms
Bacillus clausii
Bacillus subtilis
Enterogermin

Manual search of retrieved articles:*

Children | Antibiotics + *B. clausii* | Antibiotics only

Three trials retrieved:

	Benoni[2]	Puddu[3]	Destura[4]
Antibiotics + *B. clausii*	11	45	162
Antibiotics only	8	48	161
Total	19	93	323

Studies pooled:

Incidence of AAD — Fisher's exact test

435 (218 | 217)

* Controlled trials of childer 0-18 years investigating the therapeutic efficacy and safety of the commercially available probiotic drug containing a mix of the four B. clausii strains O/C, SIN, N/R, T.

Patient characteristics and trial design

Benoni[2]

Italy, 1984 | 0.25 - 2 years | **Infection:** Respiratory, Urinary

Antibiotic: Ampicillin

Antibiotics + *B. clausii*	vs	Antibiotics only
11		8

Start — ≥ 5 days — End

Puddu[3]*

Italy, 1980 | 3 - 14 years | **Infection:** Tonsils, Middle ear, Para/nasal cavities

Antibiotic: Ampicillin, Thiamphenicol, Erythromycin, Tetracycline

Antibiotics + *B. clausii*	vs	Antibiotics only
45		48

Start — 10 days — End

Destura[4]*†

Phillipines, 2008 | 0.5 - 12 years | **Infection:** Respiratory, Urinary, Skin/soft tissue

Antibiotic: Penicillin, Cephalosporin, Pen/ceph combination

Antibiotics + *B. clausii*	vs	Antibiotics only
162		161

Start — ≤ 9 days — End

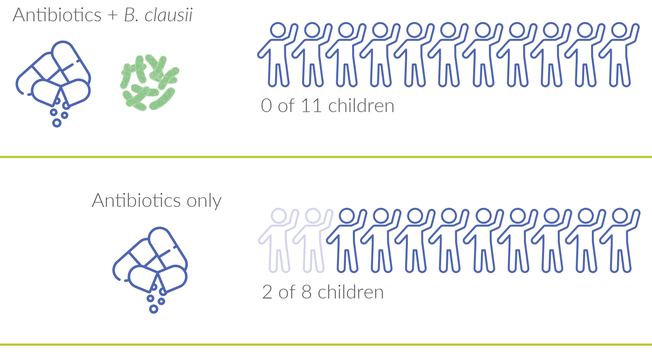
* randomised; † multicentre

RESULTS

Benoni trial[2]

- In the ampicillin-only group, therapy was suspended due to diarrhoea in 2 children, while the number of stools did not increase in the children co-treated with *B. clausii* (**Figure 1**)[2]

Figure 1: Events of diarrhoea occurring during antibiotic therapy with and without *B. clausii*.

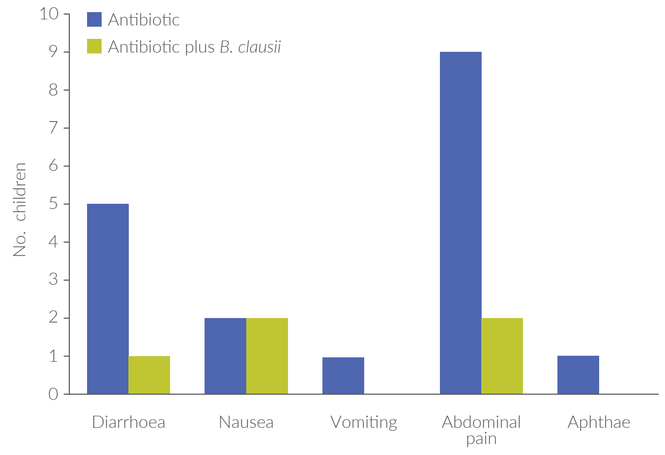


DOWNLOAD NOW

Puddu trial[3]

- Children randomised to *B. clausii* had fewer gastrointestinal symptoms (p<0.01), including diarrhoea (present in 1 child receiving *B. clausii* and 5 children receiving antibiotics only; (**Figure 2**)[3]

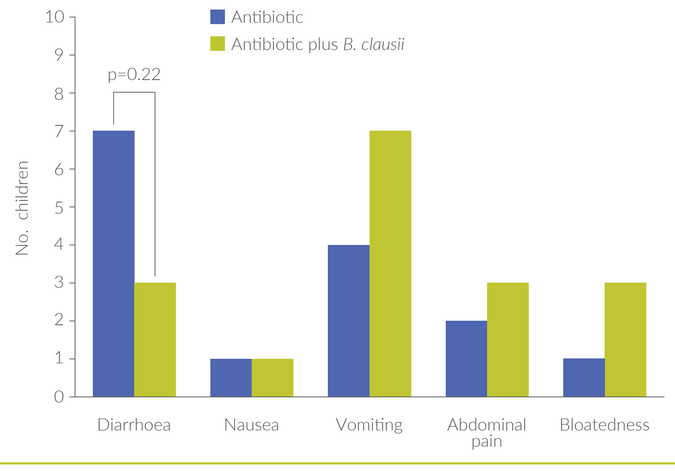
Figure 2: Gastrointestinal symptoms occurring during antibiotic therapy with and without *B. clausii*.



Destura trial[4]

- Diarrhoea occurred in 3 of 162 children receiving *B. clausii* treatment and 7 of 161 children in the control group (p=0.22; **Figure 3**)[4]

Figure 3: Gastrointestinal symptoms occurring during antibiotic therapy with and without *B. clausii*.



Pooled trials

- By combining the data of the 3 trials, a significant difference was observed (**Figure 4**)

Figure 4: Pooled re-analysis of three controlled trials of *B. clausii*. for the prevention of antibiotic-associated diarrhoea

Incidence of diarrhoea

	Antibiotics + *B. clausii*		Antibiotics only		p-value*
Benoni[2]	0%	n = 11	25%	n = 8	0.16
Puddu[3]	2%	n = 45	10%	n = 48	0.2
Destura[4]	2%	n = 162	10%	n = 161	0.22
Pooled	2%	n = 218	7%	n = 217	0.017

* Fisher's exact test

Limitations

- Inherent differences between trials such as differing duration, age ranges and methodology, whether parallel groups were present and the age of some trials.
- The trials lacked a placebo arm and were not blinded.

SUMMARY AND CONCLUSIONS

- The efficacy of *B. clausii* in the prevention of AAD in children was assessed in three clinical trials in which a lower occurrence of diarrhoea episodes was observed.
- Statistical significance was not reached in individual trials, probably because of low sample size and low overall incidence of AAD.
- Analysis of pooled results confirmed a significantly lower incidence of AAD in children receiving *B. clausii*, with a decrease from 6.5% to 1.8%, similar to the incidence observed for adults.
- **Disclosures:** All authors are employees of Sanofi.

REFERENCES

1. Nista EC et al. Aliment Pharmacol Ther 2004; 20: 11818.
2. Benoni G et al. Chemotherapia 1984; 3 (5): 2913.
3. Puddu M et al. Pediatria Intern 1980; 6: 6.
4. Destura RV 2008 unpublished data.

ACKNOWLEDGEMENTS
This work was sponsored by Sanofi. The authors also thank Ella Palmer of inScience Communications, Springer Healthcare, for providing medical writing support, which was funded by Sanofi in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

Presented at the 2019 European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) conference Glasgow, Scotland, UK.

Poster number: A-1071-0008-00867

SANOFI