

Is It Time To Recommend *Lactobacillus* for Colic? Not Necessarily

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Some infants between 1 week and 4 months of age cry a lot without an apparent reason, a phenomenon traditionally called “infant colic.” The word “colic,” derived from the Greek word for the intestine, implies that the crying is caused by gastrointestinal disorder and pain. This inference remains controversial.^{1,2} For research purposes, 1- to 4-month-old infants who cry ≥ 3 hours per 24 hours across a specified number of days are said to have colic.^{1,3}

In 2007, Savino et al³ identified promising support for a gastrointestinal explanation of the crying. In their randomized controlled trial, they found that the probiotic *Lactobacillus reuteri* reduced the crying duration of infants with colic, compared with a placebo.³ Other researchers identified gut microbiota differences between infants with colic and controls.^{4,5} Double-blind randomized controlled trials followed and led to the meta-analysis by Sung et al⁶ examined here.

In many ways, this meta-analysis⁶ is an exemplary piece of 21st-century science. Supported by an international scientific association, researchers from different institutes and countries conducted a systematic literature review and combined and analyzed the resulting data from studies in 4 countries (Italy, Poland, Australia, and Canada). The strengths of their meta-analysis include the use of an individual participant data meta-analysis method, data analysis by statisticians who are independent of the original studies, and in all 4 studies, the use of double-blinding, the same

probiotic and placebo substances and doses, the same follow-up periods, and similar measures. The authors conclude: “*L reuteri* DSM 17938 is effective in breastfed infants with colic and should be considered in this subgroup of infants with colic. The evidence of the probiotic’s effectiveness in formula-fed infants is limited.”⁶ Is that conclusion justified? Regrettably, so far as it claims *L reuteri* to be effective as a treatment for all breastfed infants with colic, the answer is no.

The individual participant data meta-analysis method works by pooling the raw data from the original studies. In the 3 studies that involved breastfed infants, researchers found that *L reuteri* DSM 17938 reduced crying in infants with colic after 21 days of treatment (the primary outcome point) as well as at 7 and 14 days. In the fourth study (the Australian study), researchers included both breastfed and formula-fed infants and revealed *L reuteri* to be ineffective in both groups. The 3 studies with positive results included 89 breastfed infants (ranging from 24 to 40 infants per study) who received *L reuteri* and 89 who received a placebo. The Australian breastfed and formula-fed data were originally combined and examined separately in subsidiary analyses without giving group numbers.⁷ Subtracting 89 from the 115 meta-analysis cases in Table 2,⁶ it appears that 26 breastfed infants from the unsuccessful Australian study were combined with the 89 infants from the 3 successful studies. Given this 1:3 ratio, the result is unsurprising.

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DOI: <https://doi.org/10.1542/peds.2017-3445>

Accepted for publication Oct 18, 2017

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The author has indicated he has no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The author has indicated he has no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2017-1811.

To cite: St James-Roberts I. Is It Time To Recommend *Lactobacillus* for Colic? Not Necessarily. *Pediatrics*. 2018;141(1):e20173445

Equally important is what recommendation clinicians should give to parents on the basis of the findings. If *L reuteri* is ineffective in Australia, why prescribe it there because it is effective in Italy, Poland, and Canada? As the authors acknowledge, infant gut microbiotas differ between countries.⁶ Indeed, they attribute the lack of *L reuteri* effectiveness in treating formula-fed infants to gut microbiota differences between breastfed and formula-fed infants. Doesn't the same logic apply when comparing breastfed infants in different countries? The implication seems to be that rather than recommending *L reuteri* treatment universally, we need to learn why the Australian infant microbiota does not respond to *L reuteri* treatment, and we need to collect evidence in countries such as the United States and the United Kingdom, which were not included in this meta-analysis.

Lastly, although *L reuteri* has been found to be safe, some parents and clinicians may prefer colic to take its usual course, rather than add a probiotic to their infant's breast milk diet. As a background, the incidence of colic in infants not given *L reuteri* declines rapidly, from ~20% in the first 6 weeks of age to 11% at 8 to 9 weeks of age and 0.6% at 10 to 12 weeks of age.⁸ To assist treatment decisions, we also need to know how long an infant's crying will last with treatment versus without treatment and how many infants will continue to cry even with treatment.

The meta-analysis does not report the number of infants who still had colic at the outcome, while the infants' age at this point averaged just 8.9 weeks. Instead, an "improvement" is defined as a 50% reduction in the baseline amount of crying. By using that criterion, it took 14 days for most (58%) probiotic-fed infants to improve, and 76%

improved by 21 days (compared with 25% and 37%, respectively, of placebo-fed infants). The implication is that in countries where most breastfed infants respond to *L reuteri*, 2 weeks of treatment are needed before the majority reduce their crying by one-half, whereas one-quarter (24%) of infants do not respond. A related consideration is whether infants who cry a lot are in pain; if so, the case for treatment is much stronger. Although that has been assumed to be the case,⁹ the evidence does not support it.^{10,11}

Researchers who recently conducted a review of meta-analysis in nutritional studies concluded the following: "The most important contribution of a meta-analysis is not necessarily the single statistical summary of effect size, but rather may be the ability to elucidate why different studies have produced different results."¹² Meta-analyses that are conducted to examine differences and consistencies in findings when probiotics are added to the diets of infants with colic should advance understanding. In the meantime, rather than prescribing *L reuteri* as a universal treatment for breastfed infants with colic, clinicians may wish to take parents' geographic location, treatment preferences, and the limitations to its effectiveness into account.

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Pediatrics 2018;141;

DOI: 10.1542/peds.2017-3445 originally published online December 26, 2017;

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Pediatrics 2018;141;

DOI: 10.1542/peds.2017-3445 originally published online December 26, 2017;

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<http://pediatrics.aappublications.org/content/141/1/e20173445>

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