Probiotics for the prevention of allergy: A systematic review and meta-analysis of randomized controlled trials

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Background: Allergic diseases are considered a health burden because of their high and constantly increasing prevalence, high direct and indirect costs, and undesirable effects on quality of life. Probiotics have been suggested as an intervention to prevent allergic diseases.

Objective: We sought to synthesize the evidence supporting use of probiotics for the prevention of allergies and inform World Allergy Organization guidelines on probiotic use.

Methods: We performed a systematic review of randomized trials assessing the effects of any probiotic administered to pregnant women, breast-feeding mothers, and/or infants.

Results: Of 2403 articles published until December 2014 identified in Cochrane Central Register of Controlled Trials, MEDLINE, and Embase, 29 studies fulfilled *a priori* specified inclusion criteria for the analyses. Probiotics reduced the risk of eczema when used by women during the last trimester of pregnancy (relative risk [RR], 0.71; 95% CI, 0.60-0.84), when used by breast-feeding mothers (RR, 0.57; 95% CI, 0.47-0.69), or when given to infants (RR, 0.80; 95% CI, 0.68-0.94). Evidence did not support an effect on other allergies, nutrition status, or incidence of adverse effects. The certainty in the evidence according to the Grading of Recommendation Assessment Development and Evaluation approach is low or very low because of the risk of bias, inconsistency and imprecision of results, and indirectness of available research.

Conclusion: Probiotics used by pregnant women or breast-feeding mothers and/or given to infants reduced the risk of eczema in infants; however, the certainty in the evidence is low. No effect was observed for the prevention of other allergic conditions. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Allergy, prevention, probiotics systematic reviews*

Allergic diseases are on the increase, and they pose a considerable burden on health care because of potentially life-threatening allergic reactions, reduced quality of life, and associated direct and indirect costs.[1-3] It is estimated that up to 20% of the population experiences an allergic condition, such as atopic dermatitis, food allergy, asthma, allergic rhinitis, and/or conjunctivitis.[4] At the same time, a decrease in infectious diseases has been observed in developed countries and is frequently associated with the increased risk for allergies, giving rise to the so-called hygiene hypothesis of allergic diseases.[3]

The composition of the gastrointestinal microbiota has been postulated to play a role in the development of allergies because it promotes potentially antiallergenic processes: T_H1-type immunity, generation of TGF (which has an essential role in suppression of T_H2-induced allergic inflammation and induction of oral tolerance), and IgA production, an essential component of mucosal immune defence.[5] The gut microbiota hypothesis suggests that alterations in those microbiota, the early and most massive source of microbial exposure, might underlie the allergic epidemic.

From this perspective, the use of probiotic supplementation seems an attractive option for the prevention and treatment of allergic diseases. Probiotics are defined as "live microorganisms which, when administered in adequate amounts as part of food, confer a health benefit on the host."[6] They can act as promoters of an adequate balance in the gut microbiota, which in turn could prevent the development of allergies.

Although randomized controlled trials and systematic reviews have evaluated the use of probiotics for the prevention and treatment of allergic diseases, they have only assessed individual outcomes or are outdated. For example, the most recent reviews on prevention assessed the use of probiotics individually on the outcomes of sensitization,[7] asthma or wheezing episodes,[8] and atopic dermatitis.[9-12] These studies have suggested a modest reduction in atopic dermatitis (eczema) and provided evidence of a mild effect in reducing sensitization. For other types of allergic conditions (ie, conjunctivitis, food allergy, and allergic rhinitis), there are insufficient data to provide conclusions. A Cochrane systematic review[12] with relevant subgroups and outcomes was published more than 7 years ago.

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Supported by the World Allergy Organization.

Disclosure of potential conflict of interest: This study was supported by the World Allergy Organization (WAO). The institution of J. L. Brożek, A. Fiocchi, J. J. Yepes-Nuñez, L. Terracciano, S. Gandhi, C. A. Cuello-Garcia, Y. Zhang, and H. J. Schünemann, has received consultancy fees from the WAO, as well as support for travel to meetings and other study-related purposes and fees for participating in review activities. A. Fiocchi has received consultancy fees from GlaxoSmithKline, as well as payment for delivering lectures from Danone. R. Pawankar received royalties from Springer and is employed by the Nippon Medical School in Tokyo, Japan, which has received or has grants pending from the Japanese Ministry of Education. L. Terracciano has received consultancy fees from Heinz-Plada. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication January 13, 2015; revised April 17, 2015; accepted for publication April 20, 2015.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2015.04.031

Abbreviations used
GRADE: Grading of Recommendation Assessment Development and Evaluation
RR: Relative risk

Probiotics have been used in the clinical setting in different ways: (1) directly given to infants as an oral preparation or with milk formula in those infants not being breast-fed; (2) indirectly given through breastmilk when given to mothers during breast-feeding; (3) transplacental when given to mothers during pregnancy; or (4) a combination of the above.

Informing the recommendations in the World Allergy Organization clinical practice guideline for the prevention of allergies or Guideline for Allergic Disease Prevention,[13] we conducted a systematic review to answer 3 clinical questions:

1. Should supplementation of probiotics versus no such supplementation be used in pregnant women to prevent development of allergy in their children?
2. Should supplementation of probiotics versus no such supplementation be used in breast-feeding mothers to prevent development of allergy in their children?
3. Should supplementation of probiotics versus no such supplementation be used in infants to prevent development of allergy?

METHODS

Criteria for considering studies for this review

Types of studies. We included randomized controlled trials with a minimum follow-up of 4 weeks that compared any type of probiotic with placebo, irrespective of their language or publication status.

Types of participants. Studies must have included 1 or more of the following groups of participants: pregnant women, breast-feeding mothers, and infants and children. We included studies that assessed the use of probiotics in any age group, from newborn infants to preschool and school-age children (up to 9 years of age).

Types of interventions. We included studies that used any probiotic supplementation, irrespective of formulation (capsules, oil droplets, suspension, and supplements in infant formulas or cereals), microorganism, supplement composition (single vs multiple strains), or dose.

Types of outcome measures. The World Allergy Organization guideline panel members in a formal process determined the outcomes of interest. The following outcomes were deemed critical to the decision whether to use probiotics for prevention of allergies: eczema, asthma and/or wheezing, food allergy, allergic rhinitis, any adverse effects, and severe adverse effects.

Search methods

We searched the Cochrane Central Register of Controlled Trials (from inception to December 2014), Ovid MEDLINE (from inception to December 2014), and Ovid Embase (from January 1980 to December 2014). We present all search strategies in Table E1 in this article's Online Repository at www.jacionline.org. We used the Cochrane highly sensitive search strategy for randomized controlled trials for retrieving citations in MEDLINE and Embase. We also contacted authors of identified studies and experts in the field to find any additional studies we had not identified by database searches, reviewed abstracts and conference proceedings, and crosschecked references of included studies for additional sources. We also searched clinicaltrials.gov for ongoing studies.

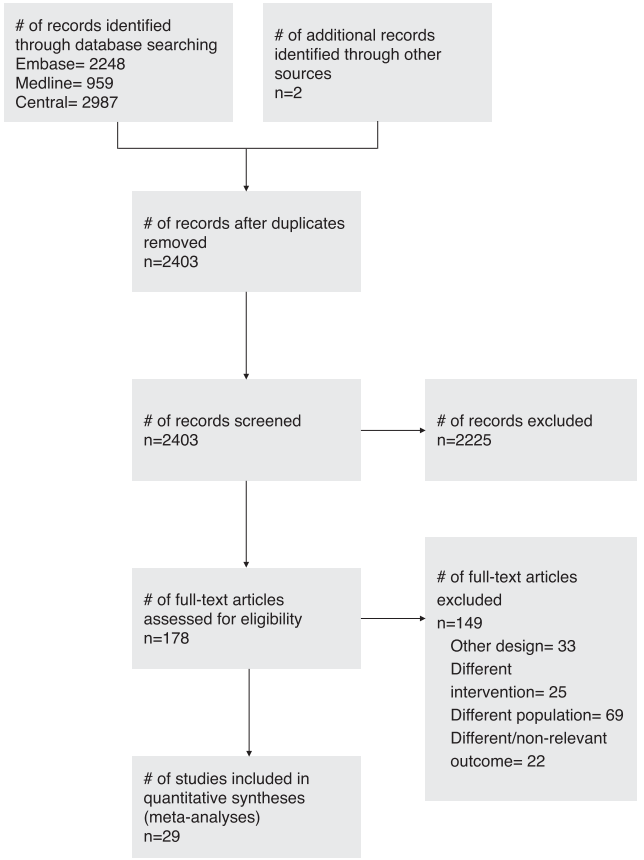

FIG 1. Study flow diagram.

Data collection and analysis

Selection of studies. Three review authors (C.A.C.-G., J.J.Y.-N., and S.G.) independently screened in duplicate the titles and abstracts identified in database searches and resolved differences by consensus. The same authors assessed full-text publication for inclusion using prepiloted screening forms. Any disagreements were resolved by consensus or by a fourth review author (J.L.B.).

Data extraction. Four review authors (C.C.G., J.J.Y.-N., S.G., and A.A.) extracted the data using predefined and piloted data extraction forms. We recorded study sequence generation, concealment of allocation, masking, exclusions, patient dropout, loss to follow-up, and noncompliance; participants' characteristics, such as country of origin and setting where participants were enrolled, number of patients in the study, number of patients randomized, age, age range, sex, and inclusion and exclusion criteria; intervention characteristics, such as type of probiotic, dosage in colony-forming units, placebo use, and duration of treatment; and individual outcomes, specifically the length of follow-up and the event rate in each of the outcomes mentioned above. We also recorded trial registration status and funding for each study. We performed data extraction in duplicate, and any discrepancies were resolved by consensus.

Assessment of risk of bias in included studies. We assessed the risk of bias in the included studies using the Cochrane Collaboration risk of bias tool.[14]

Measures of treatment effect. We estimated relative risks (RRs) and 95% CIs for dichotomous outcomes and mean differences with associated 95% CIs for continuous outcomes.

Dealing with missing data. We did not impute missing data. We contacted the study authors to obtain additional information if it was not available from the published report or reports from studies.