Probiotics for treating persistent diarrhoea in children (Protocol)

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Probiotics for treating persistent diarrhoea in children

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate probiotics for treating persistent diarrhoea in children.
BACKGROUND

The World Health Organization (WHO) defines persistent diarrhoea as an illness of proven or presumed infectious etiology that lasts 14 days or more (Anonymous 1988). Persistent diarrhoea accounts for 3% to 20% of all diarrhoeal episodes in children aged less than five years (IWGPD 1996). It is also directly responsible for between 36% and 54% of all diarrhoea-related deaths according to two large, community-based studies (Schorling 1990; Fauveau 1992). Thus, the main consequences of persistent diarrhoea are morbidity (with an increased risk of hospital admission), death, and malnutrition.

The cause of persistent diarrhoea is not known and the pathogenic mechanisms are not well understood; most of the viruses, parasites, and bacterial pathogens that cause acute diarrhoea have also been associated with persistent diarrhoea (Ochoa 2004). However, it is not known whether bowel bacterial overgrowth is a cause of persistent diarrhoea or the result of impaired immunity and/or contaminated water (Bhutta 2004). The management of persistent diarrhoea is complex because the etiology and pathogenesis are complex. It includes adequate dietary management, micronutrient supplementation, adequate rehydration, and antimicrobials (Ochoa 2004). In developing countries, where persistent diarrhoea is a problem, it is recognized that frequent recurrence of acute diarrhoeal episodes (less than 14 days’ duration) result in nutritional compromise, which is in turn the most important epidemiological risk factor for persistent diarrhoea (Bhandari 1989). Other risk factors for persistent diarrhoea include lack of breastfeeding and immune deficiencies (Bhutta 2004).

Probiotics are defined as living organisms that when administered in adequate amounts confer a health benefit on the host (Pineiro 2007). They are used widely for various indications because of their widespread acceptance and general lack of adverse effects. Probiotics most commonly used include three genera of lactic acid bacteria, namely, Lactobacillus, Bifidobacterium, and Streptococcus. Acute infectious diarrhoea is the most investigated field in the area of probiotic use in children; five recent systematic reviews have described the role of probiotics in acute infectious diarrhoea (Szajewska 2001; Huang 2002; Van Niel 2002; Allen 2003; McFarland 2006). Each review demonstrated that probiotics had a good safety profile, significantly reduced the duration of diarrhoea by 13.4 to 30.5 hours (range), reduced the frequency of diarrhoea, and reduced the duration of hospital stays. However, the effects of probiotics in acute diarrhoea are not generalizable to persistent diarrhoea.

The rationale for using probiotics to treat infectious diarrhoea is based on the assumption that they modify the composition of the intestinal microflora and act against enteric pathogens. Several possible mechanisms have been proposed: colonization resistance; production of antibacterial substances; competition for nutrients; competition for binding sites on intestinal cells; and enhancement of the immune defence system (Vandenplas 1999). Probably two or more of these mechanisms operate simultaneously, and they may differ depending on the properties of enteric pathogens (eg bacterial or viral etiology) and probiotic strain. Moreover, the beneficial effects of probiotics in acute diarrhoea in children seem to be strain-dependent, dose-dependent (greater for doses of > 10^10 colony forming units), significant in people with viral gastroenteritis, and more evident when treatment with probiotics is initiated early in the course of disease (Szajewska 2005).

OBJECTIVES

To evaluate probiotics for treating persistent diarrhoea in children.

METHODS

Criteria for considering studies for this review

Types of studies
Randomized controlled trials.

Types of participants
Children (0 to 18 years of age) with persistent diarrhoea (duration > 14 days) that is proven (pathogens isolated from stools) or presumed to be caused by an infectious agent.

Types of interventions
Intervention
Specific, identified probiotic. Trials investigating yoghurt or other fermented foods in which a specific probiotic agent is not identified are not eligible.

Control
Placebo or no treatment. Intervention and control arms to be otherwise treated identically in relation to other treatments and drugs.

Types of outcome measures
Primary
1. Duration of diarrhoea.
Secondary
1. Stool frequency.
2. Stool volume.
3. Weight-for-age z score.
4. Hospital stay.
5. Death from any cause.

Adverse events
1. Serious (leads to death, hospitalization, or disability, is life-threatening, or requires intervention to prevent permanent impairment).
3. Other.

Search methods for identification of studies
We will identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Databases
We will search the following databases using the search terms and strategy as described in Table 1: Cochrane Infectious Disease Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library; MEDLINE; EMBASE; and LILACS. We will also search the metaRegister of Controlled Trials (mRCT) using 'diarrhoea', 'probiotic*', 'lactobacill*' and 'bifidobacter*' as search terms.

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</table>

<sup>a</sup> Cochrane Infectious Disease Group Specialized Register
<sup>b</sup> MEDLINE; EMBASE; and LILACS

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Table 1. Detailed search strategies (Continued)

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aCochrane Infectious Diseases Group Specialized Register.
bSearch terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Lefebvre 2008); upper case: MeSH or EMTREE heading; lower case: free text term.

Organizations
To help identify unpublished and ongoing trials, we will contact researchers at organizations including the International Scientific Association for Probiotics and Prebiotics.

Reference lists
We will check the reference lists of all studies identified by the above methods.

Data collection and analysis
Selection of studies
Two authors (CABM and NYCP) will independently screen the search results using article titles and abstracts (if available). The full text of the selected articles will be retrieved and scrutinized to ensure that multiple publications from the same trial are included only once. The same authors (CABM and NYCP) will then independently select articles for inclusion according to a standardized form to assess the eligibility of trials. Disagreements will be resolved through discussion with a third author (GBA). The trial authors will be contacted for clarification if it is unclear whether a trial is eligible for inclusion. Excluded trials along with the reason for exclusion will be listed.

Data extraction and management
Two authors (GBA and RARG) will independently extract the data using standard forms. Any differences will be resolved through discussion with a third author (CABM). Attempts will be made to obtain any missing data from the trial authors. We aim to extract the following data: hazard ratios and standard deviations for duration of diarrhoea if trials report them, otherwise we will extract mean and standard deviations; the number of stools and the number of person days; the mean stool output from the start of the intervention; the mean weight for age z score; the mean duration of hospital stay and its standard deviations; and the number of deaths in each group. The authors will aim to carry out an intention-to-treat analysis, and extract the number of participants randomized and analysed in each group for all outcomes.

Assessment of risk of bias in included studies
Two authors (GBA and NYCP) will independently assess the risk of bias of each trial using The Cochrane Collaboration’s risk of bias tool (Higgins 2008). We will follow the guidance to make
judgements on the risk of bias in six domains: sequence generation; allocation concealment; blinding (of participants, personnel, and outcome assessors); incomplete outcome data; selective outcome reporting; and other sources of bias. We will categorize these judgements as ‘yes’ (low risk of bias), ‘no’ (high risk of bias), or ‘unclear’. Where our judgment is unclear we will attempt to contact the trial authors for clarification.

Assessment of reporting biases
We will assess publication bias using the funnel plot if there are about 10 or more trials included in a meta-analysis.

Data synthesis
We will analyse the data using Review Manager 5. Results will be combined unless diversity (clinical and methodological heterogeneity) or statistical heterogeneity (non-overlapping confidence intervals) is unreasonable. We will pool dichotomous data using the risk ratio and calculate the number needed to treat when appropriate. If continuous data are summarized by arithmetic means and standard deviation data, then we will combine them using the mean differences; where continuous data are summarized using geometric means, we will combine them on the log scale using the generic inverse variance method and report them on the natural scale. The hazard ratio will be combined on the log scale using the generic inverse variance method for time to event data. We will present all results with 95% confidence intervals. It is likely that we will need to summarize the adverse event data using the risk difference since events are likely to be rare.

Subgroup analysis and investigation of heterogeneity
Heterogeneity amongst trials will be investigated by looking at whether a graphical plot of the confidence intervals for the results of each study overlaps, using a standard chi-square test with significance set at $P < 0.10$, and using the $I^2$ test statistic (> 50% will be considered as substantial heterogeneity). Subgroup analyses will be subdivided by: identified diarrhoeal pathogens, trial low to middle income/high-income setting, probiotic strain and dosage of probiotic.

Sensitivity analysis
We will perform sensitivity analysis in order to explore whether effect size is different in adequately concealed trials compared with the rest.

ACKNOWLEDGEMENTS
The editorial base for the Cochrane Infectious Diseases Group is funded by the UK Department for International Development (DFID) for the benefit of developing countries.

REFERENCES

Additional references

Allen 2003

Anonymous 1988

Bhandari 1989

Bhutta 2004

Fauveau 1992

Higgins 2008

Huang 2002

IWGPD 1996

Lefebvre 2008

McFarland 2006

Ochoa 2004

Pineiro 2007

Review Manager 5

Schorting 1990

Szajewska 2001

Szajewska 2005

Van Niel 2002

Vandenplas 1999

* Indicates the major publication for the study

HISTORY

CONTRIBUTIONS OF AUTHORS
G Bernaola Aponte conceived the idea for this systematic review, participated with the development of the methodological aspects of the protocol, and has co-ordinated its development. CA Bada Mancilla and NY Carreazo Pariasca have helped develop the search strategy. RA Rojas Galarza gave advice regarding persistent diarrhoea.

DECLARATIONS OF INTEREST
None known.
SOURCES OF SUPPORT

Internal sources

• No sources of support supplied

External sources

• Iberoamerican Cochrane Center, Spain.