We sought to conduct a systematic review and meta-analysis of all probiotics for the treatment of community-acquired acute diarrhea specifically among children < 5 years of age. This systematic review was conducted to examine the efficacy of probiotics in diarrhea treatment and was designed to meet the needs of the Lives Saved Tool (*L ST*) [9].

Methods

We conducted a systematic literature review to identify randomized controlled trials (RCT) of probiotics for the treatment of community-acquired acute diarrhea among children < 5 years of age. We employed the Child Health Epidemiology Reference Group (CHERG) guidelines [9] and searched all published literature from PubMed, Cochrane Library, WHO Regional Databases, Web of Science, Biosis, Popline, Global Health, Scopus, and Embase for relevant literature in all available languages published before December 1, 2012. We used various combinations of the Medical Subject Heading Terms (MeSH) and all fields search terms for and . Given the wide variety of possible therapeutic probiotic microorganisms, we also searched using nomenclature variations of probiotic microorganisms (e.g., *L* , *S.* , .). If reports were unavailable for full-text abstraction, we made every effort to obtain the unpublished data from the authors. The complete search strategy is available in a WebAppendix (Additional file 1).

Inclusion/Exclusion criteria

We included RCTs conducted among children < 5 years of age with acute diarrhea defined as ≥ 3 loose or watery stools per day, and a suitable control group. A suitable control group was defined as a group that was identical to the treatment group, but received a placebo and/or the appropriate standard of care for acute diarrhea in lieu of the probiotic. We sought a representative population of community-acquired diarrhea and thus excluded studies that: a) excluded all breastfed children; b) excluded specific types of diarrhea by etiology or only focused on a specific etiology; c) included children with a history of or current antibiotic use; or d) studies that did not evaluate probiotics alone. We included studies with at least 1 of the following outcomes: mortality, hospitalizations, severity (stool frequency on day 2, as a secondary measure of severity), or diarrhea duration.

Abstraction and analysis

We abstracted all studies that met our inclusion/exclusion criteria into a standardized abstraction form (Additional file 2). We then organized abstracted data by outcome and probiotic microorganism. Abstracted variables included study design, probiotic definition and dosage, point estimates for both study arms, and relative outcome effect.
Individual study arm characteristics a6(iondditsage8(our495(of2(t

risk of hospitalization among children who received probiotics compared with placebo (RR=0.81; 95% CI: 0.42–1.57) (Table 3 & Figure 2).

Discussion

We conducted a systematic review of RCTs to estimate the effect of probiotic microorganisms for the treatment of community-acquired acute diarrhea in children. Results of this systematic review indicate that probiotics reduced stool frequency on the second day of treatment by 13.1%. When we combined all the study arms we found a 14.0% reduction in diarrhea duration among those who received probiotics compared to those who received placebo. Of the 10 study arms included in the analysis, only 1 *LGG* arm [13] and 3 probiotic mixtures [12,13,15] found a significant reduction in diarrhea duration with effect sizes of 32%, 28.5%, 39.4% and 13.9% respectively (Table 4).

Probiotics did not have an effect on the relative risk of hospitalization between children in the treatment and control groups. None of the included studies reported diarrhea deaths, thus we were limited to outcomes that reflected diarrhea morbidity. Based on the available data, relative risk of hospitalization was the best measure of severe morbidity, but this outcome had a limited number of events across the two included studies [13,17] (Table 3). None of the individual study arms reported a significant difference in hospital admissions between treatment and control groups, but studies were not powered for this outcome measure.

Despite a number of systematic reviews on the efficacy of probiotic treatment in infectious diarrhea, this is the first to apply the CHERG guidelines to estimate the effect of probiotic treatment on community-acquired acute diarrhea among children for inclusion in the *L ST* software. This review follows the CHERG systematic review methods required of all *L ST* interventions to estimate the effect of the intervention on cause-specific mortality [9]. The *L ST* tool is designed to provide international agencies and policymakers with evidence-based

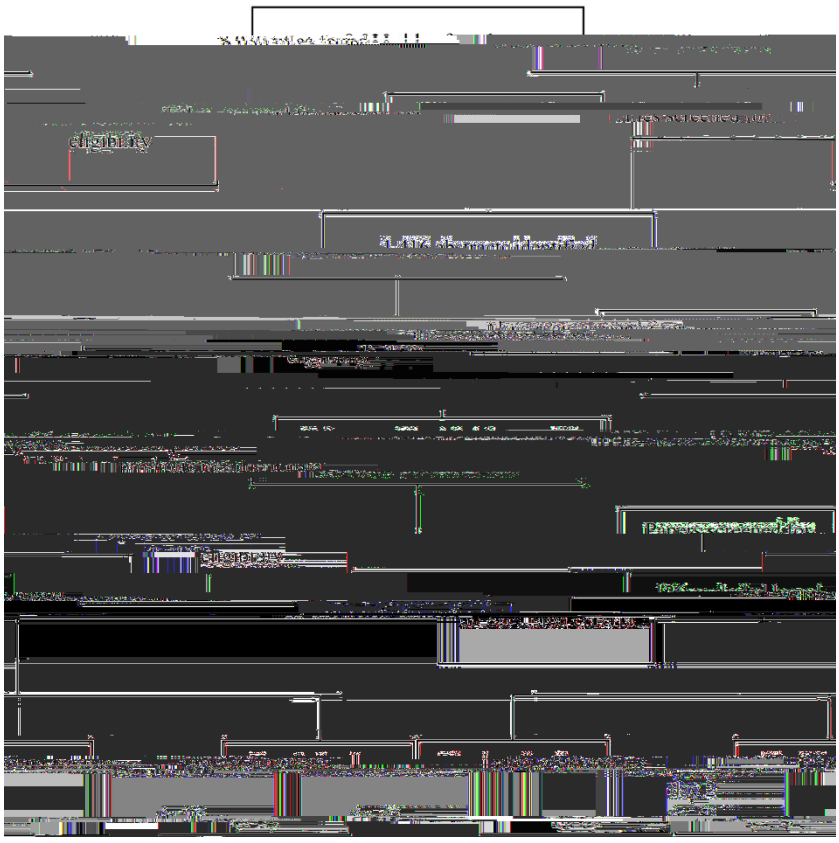

Figure 1 Results of literature search for studies on treatment of diarrhea with probiotics

Table 4 Percent difference and weight contributed by study and continuous outcome

D			
Lac bac ll r a GG	Canani [13]	-32.0*	10.2
Lac bac ll r a GG	Costa-Ribeiro [14]	-2.1	10.6
Lac bac ll r a GG	Misra [16]	-9.5	18.0
L. b gar & S. er ll	Boudraa [12]	-28.5§	9.6
Sacc ar ce b ird	Canani [13]	-9.1	9.4
Bac ll c	Canani [13]	2.2	10.2
E er c c fae	Canani [13]	0.0	9.4
L. b gar , L. ac d ll , S re c c er ll , B. b fid	Canani [13]	-39.4*	9.9
L. ac d ll & B fid bac er a fa	Lee [15]	-13.9*	8.6
Lac bac ll GG, L. ac d ll , L. ca e, L. c , B fid bac e fa	Veereman-Wauters [17]	-7.5	4.0
Lac bac ll r a GG	Canani [13]	-20.0*	12.8
Lac bac ll ac d ll	Rafeey [19]	0.0	8.6
Sacc ar ce b ird	Canani [13]	0.0	11.9
Sacc ar ce b ird	Cetina-Sauri [18]	-14.2§	14.0
Bac ll c	Canani [13]	0.0	12.8
E er c c fae	Canani [13]	0.0	11.9
L. b gar , L. ac d ll , S re c c er ll , B. b fid	Canani [13]	-20.0*	12.5
L. ac d ll & B fid bac er a fa	Lee [15]	-48.6*	10.8
Lac bac ll GG, L. ac d ll , L. ca e, L. c , B fid bac e fa	Veereman-Wauters [17]	-16.7	4.7

studies that did not exclude based on etiology. To be programmatically relevant at the community/household level

for mild outcomes (i.e., diarrhea duration and stool frequency), there is insufficient evidence to conclude probiotics for the treatment of diarrhea will reduce diarrhea mortality, and thus at this time this intervention should not be included in *L ST* (Figure 3).

Conclusions

This review highlights important implications for future research of the therapeutic effectiveness of probiotics, when compared with rehydration alone, for childhood diarrhea in LMIC. Community-based RCTs should be conducted in low- and middle-income countries to determine the effect of probiotic treatment, when compared with ORS, continued feeding, and zinc - the recommended treatment for community-acquired acute diarrhea among children <5 years of age. Furthermore, cost-effective analyses and qualitative studies should examine parental acceptance and access to probiotics to determine the feasibility of probiotic treatment in developing countries.

Additional material

Additional file 1: Medical Subject Heading Terms (MeSH) and all fields search terms for *probiotic* and *diarrhea*.

Additional file 2: Abstracted data by outcome and probiotic microorganism.

Additional file 3: Study characteristics including: treatment agent, treatment duration, standard of care, study location, age range of study population, and relevant outcomes.

List of abbreviations

CHERG: Child Health Epidemiology Reference Group; *LGG*: *Lactobacillus rhamnosus GG*; *LiST*: Lives Saved Tool; LMIC: Low- and middle-income countries; ORS: Oral rehydration salts; RCT: Randomized control trial.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JAA led the review, abstraction, analysis and initial draft of manuscript; CLFW conceptualized the study and contributed to the analysis, interpretation, and manuscript preparation. RA conducted the initial literature search, contributed to the data abstraction, and reviewed the final manuscript. REB advised on the overall study design and methodology and contributed to the manuscript.

Acknowledgements

We would like to acknowledge Laura Lamberti for her assistance in performing the meta-analysis. We also would like to thank Mary K. Charles, Mengying Li and Nino Paichadze for their assistance in screening the foreign language articles for inclusion in this review. Additionally, thank you to Peggy Gross, a public-health informationist with the Johns Hopkins Welch Medical Library, for her contributions to the literature search for this systematic review.

Publication info

The publication costs for this supplement were funded by a grant from the Bill & Melinda Gates Foundation to the US Fund for UNICEF (grant 43386 to "