Global Interventions for Children with Comorbid Diarrhea and Acute Malnutrition: a Systematic Review

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Abstract

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Globally, more than half a million children die each year from diarrhea, mostly in low- and middle-income countries (LMICs). Young children with acute malnutrition, are at particularly high-risk of death. Current diarrhea management strategies for children presenting to medical care for diarrhea in LMICs focus primarily on the management of acute illness which have important benefits for reducing acute diarrheal disease severity, recurrence and mortality risk, but the evidence to support their impact on improving longer term outcomes is limited. An electronic literature search was performed to identify randomized controlled trials (RCTs) published between January 1, 1980 and March 31, 2020 in Pubmed. Search terms relating to wasting, diarrhea and/or dysentery, and treatment/interventions were used with filters related to clinical trials, locations (in low- and middle-income settings, and age groups (under 18 years). The predefined search criteria yielded a total of 197 articles. After exclusions at the title, abstract, and full-text stages, 17 articles containing interventions for managing diarrhea and malnutrition in children. The 17 trials included eight food-based interventions, four probiotic interventions, three Vitamin A studies, and two antibiotic studies. While there are some promising interventions, such as probiotics and some

food-based interventions, adequately powered, double-blind, placebo-controlled trials are needed before recommendations to guidelines can be made. Further, the paucity of evidence conducted recently highlights the need to generate evidence that is likely to improve outcomes in children living in LMICs today and in the near future

Specific Aims

Globally, more than half a million children die each year from diarrhea, mostly in low- and middle-income countries (LMICs).[1] Young children with acute malnutrition, defined as two or more standard deviations below the mean weight for height of a reference population, mid-upper arm circumference (MUAC) of less than 12.5 cm in over 6 month olds, or presence of edema, are at particularly high-risk of death.[2] Children who survive diarrheal episodes are at increased risk of subsequent diarrheal episodes, enteric dysfunction, and nutritional deterioration.[3,4]These consequences of diarrhea, in turn, have long-term impacts on school performance, cognitive development, and earning potential. [5-7]

Current diarrhea management strategies for children presenting to medical care for diarrhea in LMICs focus primarily on the management of acute illness, i.e., dehydration with oral or intravenous rehydration, zinc replacement, and antibiotic therapy for suspected shigellosis or cholera.[8] While these interventions have important benefits for reducing acute diarrheal disease severity, recurrence and mortality risk, the evidence to support their impact on improving longer term outcomes is limited.[9] The World Health Organization (WHO) guidelines for management of children with *severe* acute malnutrition (SAM), defined as weight-for-height z-score (WHZ) <-3, nutritional edema, or MUAC less than 11.5cm in over 6 month old) include therapeutic feeding, vitamin A supplementation, and antibiotic treatment (for complicated SAM). Specific to the management of diarrhea, rehydration of children with SAM is recommended to be with a lower sodium and higher potassium oral rehydration solution due to the potential risk of fluid overload, and subsequent cardiac failure.[10] Guidelines around management of children with moderate acute malnutrition (MAM), WHZ < -2 or MUAC between 11.5 and 12.5cm in over 6 month olds, a group also at high risk of poor diarrhea outcomes, are less clearly specified and do not include specific diarrhea management interventions. [2,11]

Children with comorbid diarrhea and acute malnutrition may require unique interventions due to the impact that malnutrition has on a child's physiology. For example, ReSoMal is a lower sodium and higher potassium oral rehydration solution rehydration solution that was specifically formulated for use in patients with SAM, although recent evidence calls into question its effectiveness and safety.[12] Other potential management interventions, such as antibiotics and probiotics, may have unique benefits or harms in acutely malnourished children. For example, children with SAM are at higher risk of bacterial translocation which could pose a safety concern for probiotics, in children with SAM.[13] Conversely, because children with acute malnutrition are more likely to have a disrupted or immature gut microbiome, re-colonization of beneficial gut bacteria, from probiotic therapy, may be particularly effective in this population.[14] Reviews of novel diarrhea management interventions, other than those for rehydration[12], have not been evaluated for specific nutritional and diarrheal outcomes in acutely malnourished children, a population most likely to benefit from such interventions.

Novel interventions, and a synthesis of evidence, are needed to optimally advise management of diarrhea with comorbid malnutrition among children living in LMICs. Taking these factors into consideration, we propose a systematic review to better understand interventions (other than those for rehydration) that aim to optimize the management of children (<18 years of age) in LMICs with diarrhea and wasting.

This systematic review addressed the following specific aims:

1) To determine the efficacy (in terms of mortality, diarrhea morbidity, and nutritional status) of current WHO-recommended interventions for diarrhea management (e.g. zinc and antibiotics for suspected shigellosis and cholera) among children with diarrhea and comorbid acute malnutrition residing in LMICs.

2) To determine the efficacy (in terms of mortality, diarrhea morbidity, and nutritional status) of other interventions for diarrhea management (probiotics, prebiotics, antibiotics other than for suspected *Shigella* and cholera, other nutritional supplements) among children with diarrhea and acute malnutrition residing in LMICs.

Background and Significance

Diarrhea contributes to 10% of years of potential lives lost due to premature mortality or disability-adjusted life years (DALYs) for children living in LMICs. Although there has been significant progress made towards reducing under 5 mortality attributed to diarrhea over the last 20 years, from 441 per 100,000 in 1990 to 114 per 100,000 in 2017[15]; the fact that half a million children still die each year highlights the need for continued investment and innovation around diarrhea management strategies. More than half of these deaths are among children who received rehydration therapy,[16] the cornerstone of diarrhea management. Continuing to reduce diarrhea deaths will require targeting interventions to children at highest fatality risk and those with comorbidities for whom standard diarrhea management interventions may not be as effective.

Children with acute malnutrition (defined as WHZ <-2 standard deviations from the mean or MUAC < 12.5 cm in under 6 months olds) are at a more than 10-times higher risk of dying from moderate-to-severe diarrhea (MSD) than children with MSD but without acute malnutrition.[2] The Global Burden of Disease Study estimated that acute malnutrition is the second most important risk factor for diarrhea-associated mortality, second only to unsafe sanitation.[15] In addition to increasing risk of death following diarrhea, children with comorbid acute malnutrition are at increased risk of diarrhea recurrence and further nutritional deterioration following a diarrheal episode than children with diarrhea who are not malnourished.[3] This compounding risk makes children with comorbid acute malnutrition and diarrhea a population in need of targeted interventions.

The underlying mechanism of increased vulnerability to poor outcome from diarrhea among malnourished children is not fully elucidated, but may be due to immune system compromise secondary to underlying malnutrition, increased gut permability[17] leading to bacterial translocation, or an immature gut microbiome[14] which influences local and systemic immunity. These mechanisms provide opportunities and challenges for the management of diarrhea in children with wasting.

The current standard of facility-based care for management of diarrhea in children living in LMICs is to manage any dehydration with IV or oral fluids, provide 10-14 days of therapeutic zinc to reduce diarrhea duration and recurrence[18], counsel on continued feeding, and provide antibiotic therapy for dysentery or suspected cholera.[19] For children hospitalized with complicated severe acute malnutrition, Resomal – an ORS specifically formulated to address sodium excess and hypokalemia is recommended. Nutritional management of complicated SAM starts with therapeutic milk (F-75 then F-100) followed by ready-to-use therapeutic food, whether children present with diarrhea or not. Antibiotics are also recommended irrespective of whether or not they have diarrhea (Table 1). There are no additional diarrhea management guidelines specific to children with SAM, nor are there unique guidelines for the management of diarrhea in children with MAM. Given the unique gut, immune, and other physiological-related disturbances that acutely malnourished children suffer from[20], and their higher frequency of diarrheal episodes, these children may benefit from modified or unique interventions particularly targeting these vulnerabilities when presenting to care with diarrhea.

Finding new and innovative interventions for children with comorbid diarrhea and acute malnutrition is incredibly important to reduce deaths globally. Because diarrhea and acute malnutrition are interdependent risk factors, along with many other diseases, children can be stuck in an unfortunate cycle of illness that increases years lived with disability and risk of mortality. With that in mind, identifying adequate interventions that work in diverse settings in combatting these comorbidities is imperative.

Table 1. Recommended management for children presenting with diarrhea and acute malnutrition according to the World Health Organization[10,19,21]

Recommendation	Strength of Recommendation
Children with severe acute malnutrition who present with either acute or persistent diarrhea, can be given ready-to-use therapeutic food in the same way as children without diarrhea, whether they are being managed as inpatients or outpatients	*strong recommendation, very low-quality evidence*
Children with severe acute malnutrition who present with some dehydration or severe dehydration at time of diarrhea presentation should receive either ReSoMal half-strength standard WHO low-osmolarity oral rehydration solution with added potassium and glucose, unless the child has cholera or profuse watery diarrhea Such children should be given standard WHO low- osmolarity oral rehydration solution that is normally made, i.e. not further diluted	*strong recommendation, low quality evidence*
Children with uncomplicated severe acute malnutrition, not requiring hospital admission and who are managed as outpatients, should be given a course of oral antibiotic such as amoxicillin	*Condition recommendation, low quality evidence*
Children with severe acute malnutrition should receive the daily recommended nutrient intake of vitamin A throughout the treatment period. Children with severe acute mal- nutrition should be provided with 5000 IU vitamin A daily, either as an integral part of therapeutic foods (F-75/F-100) or as part of a multi-micronutrient formulation	*Strong recommendation, low quality evidence*
All children under the age of 5 with diarrhea should receive 10-14 days of oral therapeutic zinc.	*Not reported*
If cysts or trophozoites of Giardia lamblia are found, give metronidazole (7.5 mg/kg every 8 h for 7 days). Treat with metronidazole if stool microscopy cannot be undertaken or if there is only clinical suspicion of giardiasis.	*Not reported*

Methods

The guidelines set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) will be followed where possible. An electronic literature search was performed to identify randomized controlled trials (RCTs) published between January 1, 1980 and March 31, 2020 in Pubmed. Search terms relating to wasting, diarrhea and/or dysentery, and treatment/interventions were used with filters related to clinical trials, locations (in low- and middle-

income settings, and age groups (under 18 years). MESH/subject headings were also used where possible. The full list of search terms are as follows.

> ("Diarrhea"[Mesh] OR ("infantile diarrhea"[All Fields] OR "diarrhea, infantile"[MeSH Terms] OR ("diarrhea"[All Fields] AND "infantile"[All Fields]) OR "infantile diarrhea"[All Fields] OR ("infantile"[All Fields] AND "diarrhea"[All Fields])) OR ("dysentery"[MeSH Terms] OR "dysentery"[All Fields]) OR ("diarrhea"[All Fields] OR "diarrhea"[MeSH Terms] OR "diarrhea"[All Fields])) AND ("Malnutrition"[Mesh] OR ("malnutrition"[MeSH Terms] OR "malnutrition"[All Fields] OR ("nutritional"[All Fields] AND "deficiency"[All Fields]) OR "nutritional deficiency"[All Fields]) OR ("malnutrition"[MeSH Terms] OR "malnutrition"[All Fields] OR "undernutrition"[All Fields]) OR ("malnutrition"[MeSH Terms] OR "malnutrition"[All Fields] OR "malnourishment"[All Fields]) OR ("malnutrition"[MeSH Terms] OR "malnutrition"[All Fields]) OR ("cachexia"[MeSH Terms] OR "cachexia"[All Fields] OR "wasting"[All Fields]) OR (acute[All Fields] AND ("malnutrition"[MeSH Terms] OR "malnutrition"[All Fields]))) AND ((Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp]) AND (English[lang] OR Spanish[lang]) AND ("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms]) AND ("1980/01/01"[PDAT] : "2020/03/31"[PDAT]) AND "humans"[MeSH Terms])

The search was limited to journal articles reporting trials conducted in children under 18 published in English and Spanish language. The reference lists of relevant systematic reviews were examined for potentially relevant studies not identified through the database search. Trials focused on rehydration strategies, such as ReSoMal, were excluded because that literature has been synthesized previously.[12]

All titles and abstracts were reviewed by a single reviewer for potential eligibility and full text reviewed, when considered eligible, at the title/abstract stage. Journal articles were excluded if they do not meet the following criteria: randomized controlled trial of interventions for children with diarrhea, in children less than 18 years, low- and middle-income country setting, and are conducted in children with comorbid diarrhea and wasting (or report findings in this population in stratified analyses). Finally, full text articles were excluded if they did not report one or more of the following outcomes by intervention arm: mortality, diarrhea duration, diarrhea recurrence, diarrhea frequency, diarrhea recovery by pre-specified time, change in HAZ/LAZ, change in WHZ/LHZ, weight gain, change in MUAC, proportion with MAM, proportion with SAM. Reasons for exclusion based on abstract/full text were documented.

The following items were abstracted from included trials: Title, year, intervention, control/comparator group, population, sample size, duration of follow-up, and estimates of effect for each reported outcome. While there was no formal quality assessment, we abstracted key quality components of the Grading of Recommendations Assessment Development and Evaluation (GRADE) [22], such as blinding, sample size, blinding/ allocation concealment and comment on these components in the synthesis of studies.

Results

The predefined search criteria yielded a total of 197 articles. From those 197, 37 (18.8%) were excluded at the title stage, 97 (49.2%) were excluded at the abstract stage, and 46 (22.8%) were excluded at the full-text stage, leaving 17 randomized control trials that were included (Figure 1). Of the 142 articles that were excluded during the abstract and full-text stages, the reasons for exclusion were: the study was not in a population of children with comorbid acute malnutrition and diarrhea (44%), the trial was focused on prevention instead of treatment (25%),

the study did not present the outcomes of interest (8%), the study was not done in a low- or middle-income country (12%), or the study was testing a rehydration therapy (11%).

The 17 included trials tested a wide range of interventions in children presenting to health facilities with diarrhea and malnutrition (Table 2). Eight of the studies (50%) were food-based interventions including different feeding techniques (intermittent and bolus feeding) as well as different diets (for example chicken-based, maize porridge, different types of formula, fermented milk.) Four studies (22%) evaluated a probiotic intervention (*Lactobacillus rhamnosus* GG, *Lactobacillus casei*, *Lactobacillus acidophilus*, and *Bifidobacterium*). Three of the studies (17%) evaluated Vitamin A while two of the studies (11%) were focused on antibiotic treatment (nitazoxanide and gentamicin). Two (11%) of the trials were placebo-controlled whereas the remaining 15 trials compared one intervention to a standard of care (for example, WHO-approved oral rehydration treatment, standard diet, standard SAM management, low dose Vitamin A). More than half of the studies (53%) blinded participants to the study interventions and all of those were double-blind, with 47% of total studies not blinded in any way.

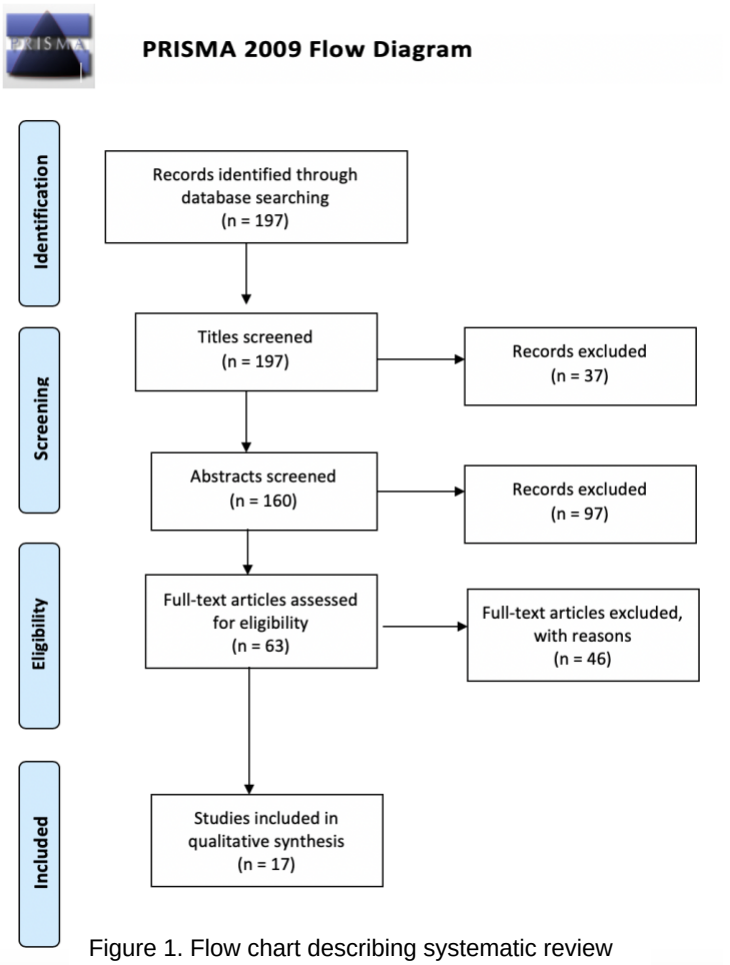

Figure 1. Flow chart describing systematic review

Trials were primarily conducted in Southeast Asia (39%), most commonly in Bangladesh (43% of the 7 conducted in Southeast Asia); Sub-Saharan Africa (27%), and Latin America (27%) (Table 1). While the search defined the dates of publication between 1980 and 2020, more than half of the trials (55%) were conducted before 2000. In the food-based intervention group, 78% of the included studies were done before 2000. The greatest number of recent trials were two Vitamin A trials and the four probiotic trials which were conducted in Bangladesh, India, and Argentina. Most trials (62%) were conducted among less than 200 children. The largest trial, a trial of Vitamin A, included 900 children.

While our eligibility criteria included trials conducted among children between 0 and 18 years, the majority (67%) were among children less than 59 months of age. Included trials were comprised of pediatric populations with variable types of diarrhea and malnutrition. Five of the 18 trials included children with only acute watery diarrhea with another 5 included only persistent diarrhea, 1 trial was among children with chronic diarrhea, and 7 not specifying. Trials including children with persistent diarrhea were more likely to be testing food-based interventions than trials including only acute diarrhea. The definition of acute malnutrition varied by study, with five studies specifying SAM, three including both SAM and MAM, while the remaining nine trials were a mixture of both and other definitions of acute malnutrition like kwashiorkor and edema (but without

also including WHZ or MUAC as part of their definition). In many studies, acute malnutrition was defined according to WHO guidelines as WHZ < -2. However, the definition from the Indian Academy of Pediatrics, where they use a grade scale (Grade I, II, III, and IV based on percentage of expected weight based on age and gender), was used in the studies conducted in Southeast Asia.

Generally, the most common outcomes within the included studies were weight gain, duration of diarrhea, days with diarrhea, and diarrhea frequency. These are defined as length in hours or days with watery stool and days with 3 or more liquid stools respectively. Similarly, stool frequency was an outcome reported in many studies. Stool frequency was defined as number of watery stools per day. Only one study, a trial of antibiotic therapy in children with and without HIV-infection, evaluated mortality as an outcome.[22] The main growth outcome reported was weight gain/change between enrollment and follow-up. Only one study reported changes in WHZ and WAZ and another was number of days to reach 80% median weight for length.

Of the food-based interventions, some, but not all studies showed at least some sign of benefit associated with the intervention (Table 1). The only trial that reported increase in WHZ and WAZ, an amino acid-based elemental feed intervention, saw significant increases of 1.77 and 1.23 in z-scores, respectively, in the intervention group when compared to a group receiving the standard nutritional rehabilitation therapy ($p < 0.001$, $p = 0.02$).[23] Khitchri, a rice-lentil mix, showed significant weight gain in the control group, which was a full-strength soy formula, so the trial was ended at its midpoint evaluation due to lack of benefit of Khitchri.[24] There were two chicken-based interventions. The chicken-based formula showed a very small difference in number of days with liquid stools between the intervention and control (a similar formula with hydrolyzed lactalbumin as a protein source) for the intervention and control groups but did not report statistical significance.[25] The chicken-based diet when compared with elemental and soy diets also presented results that were not significantly different (3.2 vs. 3.4 stools/day). The tempe-yellow maize porridge intervention yielded statistically significant improvements in weight gain (5.2 kg/day compared to 2.2 kg/day, $p < 0.05$) and decreased diarrhea duration (0.7 days compared to 4.6 days, $p < 0.05$).[26] In this study, the comparison group was children receiving milk-yellow maize porridge. The partially hydrolyzed guar gum supplement intervention led to a decrease of diarrhea in the intervention group (57 hours compared to 75 hours where $p = 0.01$).[27] Finally, a trial testing fermented milk compared to regular milk in children with diarrhea (48% of whom were acutely malnourished), found diarrhea days to be significantly decreased with 1.56 days in the intervention group and 9.17 days in the control group ($p < 0.001$).[28]

Two of the four probiotic interventions found statistically significant benefit. Both trials were studying the effects of ORS with *Lactobacillus rhamnosus* GG compared to standard ORS. The first trial found a significant decrease in diarrhea duration from 7.23 days in the control group to 5.02 days in the intervention group ($p < 0.01$).[29] The other trial showing significant results saw an average of 9.2 days in the control group and 5.3 days in the intervention group ($p < 0.05$).[30] The two probiotics interventions that did not find a statistically significant effect were a fermented milk formula with *Lactobacillus casei* and maltodextrin with *Lactobacillus rhamnosus* GG. The fermented milk probiotic trial did not have a comparison group and did not report any type of statistical analysis. The maltodextrin with *Lactobacillus rhamnosus* GG compared to a control group being managed using standard WHO guidelines did not show significant results. Antibiotics showed only one intervention that had a statistically significant reduction in mortality in HIV negative children. The intervention group, comprised of 25 children received a 3-day course of nitazoxanide, had zero deaths, while the placebo group comprised of 25 children, had four deaths ($p = 0.041$).[22] The Vitamin A interventions did not show any statistically significant improvements compared to low dose or standard of care in terms of diarrhea nor weight outcomes.

Discussion

Children with comorbid acute malnutrition and diarrhea are a high-risk population in whom interventions are needed to improve diarrhea, growth, and mortality outcomes. This systematic review identified a number of trials conducted in this population, but most were conducted over 20 years ago with small sample sizes - making the implications to current children unknown. While some interventions showed promise - namely maize porridge, different elemental feeds and some probiotics, more trials are needed, in larger, more recent populations, in order to influence guidelines of this vulnerable population.

Notably, this systematic review put no restrictions on the types of interventions, other than rehydration, yet resulted in relatively few clinical trials of interventions for the management of diarrhea and nutritional sequelae in children with acute malnutrition. Given acute malnutrition contributes disproportionately to deaths attributed to diarrhea, this relatively sparse evidence is concerning. We found that the majority of trials included children with SAM and not with MAM, and given MAM is more common and has less clear management guidance, trials recruiting children with MAM would be an important addition to the evidence base.

Some food-based interventions, particularly elemental feeds seemed to be associated with improved diarrheal and malnutrition outcomes. For example, the chicken-based and maize-based diets presented statistically significant improvements in diarrhea and malnutrition outcomes when compared to control groups. They also have the added benefit of being more sustainable options as both diets are easily made at home. However, many of these trials were conducted over 20 years ago. The availability and acceptability of these foods and their nutritional value may have changed over this period. The development and the effectiveness of these types of interventions in the current age need to be evaluated to better serve this population.

Recent clinical trial evidence in the United States have found probiotics do not improve outcomes in children with diarrhea.[31] In the probiotic trials included in this review, the two of *Lactobacillus rhamnosus* GG found an improvement in diarrhea duration associated with probiotic use whereas the other two probiotic trials found no benefit. The inconsistent benefit of probiotics may have to do with the type of probiotics being examined, length of antibiotic course, underlying health conditions of children, or underlying cause of the diarrhea. Because of previous evidence demonstrating that diarrhea was associated with a disruption in the gut microbiome,[32] and evidence that acute malnutrition also disrupted this important system,[14] the replacement of beneficial gut bacteria into the enteric system through probiotics is an intervention with strong biologic plausibility, but inconsistently supported by clinical trial evidence. Further, more evidence of the safety of probiotics, particularly in populations such as children with acute malnutrition, are needed before this intervention can be scaled if found to be effective.

Although only assessed in two trials, antibiotics were not associated with statistically significant diarrhea or nutrition outcomes in either trial. Antibiotics are also a controversial intervention because antibiotic resistance is a global health threat.[33] Antibiotics may also be a costlier intervention than interventions that can be made at home, like food-based interventions. Also, children with SAM are recommended to be on antibiotics for 2 to 7 days depending on the chosen antibiotic as part of the WHO guidelines, therefore it's unclear whether there would be added benefit of additional antibiotics in this population. Similarly, children with HIV-infection, who often also suffer from acute malnutrition, are recommended to take the prophylactic antibiotic cotrimoxazole throughout their lives, therefore an additional antibiotic may not be useful.[34] The combination of not observing benefits of antibiotics in the included trials, and existing guidelines around longer term antibiotic use in children with SAM, we did not find evidence to suggest that additional antibiotics would be beneficial in children with comorbid diarrhea and acute malnutrition.

The Vitamin A trials presented some mixed results that also require further research. Vitamin A seemed to generally result in similar outcomes as the comparator group, whether the

comparator was low dose vitamin A or standard of care. Generally, Vitamin A does not seem to be associated with clinical or nutritional benefit in this population.

This systematic review had a number of limitations. Due to COVID-19 and associated delays, only one reviewer conducted title/abstract and full text searches and abstract information from included articles. Having two independent reviewers helps ensure eligible articles are not missed and that there is a check-in for each step in the review/abstraction process. By only including English and Spanish articles in the article search we may have excluded otherwise eligible articles and in doing so, miss important evidence that may have been relevant. By only including articles published in PubMed in this review, we also may not have captured all relevant studies that have been conducted. Therefore, the articles included in this review may not full reflect the true state of the evidence, potentially with a bias towards including studies that found a statistically significant effect. Additionally, we only abstracted outcomes related to diarrhea recovery and change in nutritional status and therefore may have missed other important benefits/ harms associated with tested interventions.

Despite these limitations, this systematic review is the first, to our knowledge, to specifically address the evidence gap for managing diarrhea in children with acute malnutrition. These two conditions are inter-linked and are both associated with poor health and economic outcomes which have tremendous impact on families and countries as a whole. While there are some promising interventions, such as probiotics and some food-based interventions, adequately powered, double-blind, placebo-controlled trials are needed before recommendations to guidelines can be made. Further, the paucity of evidence conducted recently highlights the need to generate evidence that is likely to improve outcomes in children living in LMICs today and in the near future. Despite there not being clear evidence of one or more intervention(s) that are likely to be beneficial, there were many gaps highlighted throughout the discussion that propose intriguing points for future research. As new evidence is generated, guidelines for the management of children with diarrhea and acute malnutrition should be prioritized to avert the high rates of poor outcomes in this population.

	Reference	Country	Year of Enrollment	Age and sex	Type of Diarrhea (acute, persistent, dysentery)	Type of acute malnutrition (severe, moderate, both)	% of pop malnourished	% of pop with diarrhea	Total sample size	Length of Follow-up	Intervention	Comparator	Blinding?	Outcomes	Estimates of Effect
Food based	Amadi B, et. al. (2005) [23]	Zambia	1998	6-24 months males and females	persistent diarrhea	Underweight, marasmus, kwashiorkor	100%	100%	200	4 weeks	amino acid-based elemental feed	full standard nutritional rehabilitation therapy	No	Weight gain	intv = 1.7 kg, control = 1.2 kg (p = 0.002)
														increase in WAZ	intv = 1.23 control = 0.87 (p = 0.002)
														increase in WHZ	intv = 1.77, control - 1.23 (p < 0.001)
	[24]Bhutta ZA, et. al (1994)	Pakistan	<1994	6-36 months males	Persistent diarrhea	both	100%	100%	51	concluded at midterm eval	khitchri, rice-lentil mix, yogurt, and half strength buffalo milk	full-strength soy formula	No	weight gain	intv = 4.3 kg, control = 11.6 kg (p < 0.02)
														stool frequency	intv = 5.5/day, control = 4.0/day (NS)
	Eichenberger JR, et. al (1984)[35]	Brazil	<1984	1-11 months males and females	Acute	Unspecified	50%	100%	38	Unspecified	semi-elemental diet	proprietary formulas or diluted cow's milk with carbohydrates	No	weight change	Outcomes only reported graphically
	Godard C, et. al. (1989)[25]	Bolivia	1989	10-28 months males and females	Protracted diarrhea	severe	100%	100%	51	until discharge	chicken-based formula	hydrolyzed lactalbumin	No	number of days with liquid stools	intv = 6.0 days, control = 5.5 days (NR)
	Kalavi FN, et. al (1996)[26]	Kenya	1992	6-60 months males and females	Unspecified	Kwashiorkor, marasmus	100%	62%	117	2 months	tempe-yellow maize porridge	milk-yellow maize porridge	No	weight gain	intv = 5.2 kg/day, control = 2.2 kg/day (p < 0.05)
														duration of diarrheal episode	intv = 0.7 days, control = 4.6 days (p < 0.05)
	Alam NH, et. al. (2015)[27]	Bangladesh	2007	6-36 months males and females	acute watery diarrhea	severe	100%	100%	126	7 days	partially hydrolyzed guar gum supplement	children receiving WHO-ORS alone	yes	duration of diarrhea (hours)	intv = 57, control = 75 (p = 0.01)
														time required to attain 80% of median weight for length (days)	intv = 4.5, control = 5.7 (p = 0.027)

	Nurko S, et. al. (1997)[36]	Mexico	1996	3-36 months males and females	persistent diarrhea	severe	100%	100%	56	90 days	chicken-based diet	elemental and soy diets (vivonex and nursoy)	yes	mean stools/day	intv = 3.2, control1 = 3.4, control2 = 2.5 (NS)
														weight gain (g)	intv = 561, control1 = 461, control2 = 527 (NS)
	Rio ME, et. al (2004)[28]	Argentina	<2004	6-24 months males and females	unspecified	both	48%	100%	119	90 days	fermented milk	regular milk	yes	diarrhea days	intv = 1.56, control = 9.17 (p < 0.001)
Probiotics	Basu S, et. al (2009)[29]	India	<2009	Age not specified, males and females	acute watery diarrhea	protein energy malnutrition (weight for age < 80%)	60%	100%	559	4 weeks	ORS with lactobacillus rhamnosus GG (10^10 cfu and 10^12 cfu)	children on standard ORS	yes	average duration of diarrhea (days)	intv1 = 5.02, intv2 = 5.12, control = 7.23 (p = 0.000)
	Basu S, et. al (2007)[30]	India	2004	Age not specified, males and females	persistent diarrhea	protein energy malnutrition (weight for age < 80%)	90%	100%	235	4 weeks	ORS with lactobacillus rhamnosus GG (10^10 cfu and 10^12 cfu)	children on standard ORS	yes	average duration of diarrhea	intv = 5.3, control = 9.2 (p<0.05)
	Gonzalez SN, et. al. (1994)[37]	Argentina	<1994	4-24 months males and females	persistent diarrhea	unspecified	23%	100%	13	15 days	fermented milk with lactobacillus casei and lactobacillus acidophilus	none	no	diarrhea days	intv = 72.7 (NR)
	Grenov B, et. al. (2017)[38]	Uganda	2015	6-59 months males and females	acute	severe	100%	61%	400	3 months	probiotics (maltodextrin w/ LGG or BB-12)	standard management for SAM	yes	diarrhea days	intv = 6.9 days, control = 6.5 days (inpatient) (p = 0.69)
														weight gain (g/kg bodyweight per day)	intv = 6.5, control = 6.1 (p = 0.49) (inpatient)
Antibiotics	Amadi B, et. al (2001)[22]	Zambia	2001	children older than 1 year, males and females	unspecified	unspecified	79%	100%	100	5 days	3-day course of nitazoxanide	placebo control group	yes	mean duration of diarrhea in HIV positive children	intb = 44.0, control = 55.0 (NS)
														mean duration of diarrhea in HIV negative children	intv = 24.28, control = 15.29 (NS)
														mortality rate in HIV positive children	intv = 5/25, control 4/24 (NS)

														mortality rate in HIV negative children	intv = 0/25, control = 4/22 (p = 0.041)
	Khan AM, et. al. (2006)[39]	Bangladesh	<2004	6-60 months males and females	unspecified	moderate and severe	100%	100%	310	x	once-daily dose of gentamicin (5 mg/kg/day)	thrice-daily dose of gentamicin (5 mg/kg/day)	no	good clinical response	intv = 64%, control = 54% (p = 0.08)
Vitamins	Dewan V, et. al. (1995)[40]	India	1993	6-60 months males and females	acute	moderate	not reported	100%	216	10 days	vitamin A supplementation	standard management	no	duration of diarrhea (hours)	intv = 78.71, control = 100.66 (p = 0.31)
	Donnen P, et. al. (1998)[41]	Democratic Republic of the Congo	1996	0-72 months males and females	unspecified	severe	69%	100%	900	6 months	high-dose & low-dose vitamin A supplementation	placebo control group	yes	duration of diarrhea	not significantly different
	Sattar S, et. al. (2012)[42]	Bangladesh	2007	6-59 months males and females	unspecified	edema	50%	100%	260	6 months	high dose vitamin A	low-dose vitamin A	yes	diarrhea duration (hours)	intv = 73.9, control = 64.6 (p = 0.071)
														weight gain(kg)	intv = 0.74, control = 0.69 (p = 1)

Table 2: Trial characteristics and findings from 18 included studies

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