Appendix 12

Question 8: data extraction tables

Doherty *et al.* 1998[68]

Data extraction table

Reference and design	Intervention	Participants	Outcome measures
Author: Doherty *et al.*[68] *Year:* 1998 *Linked paper:* Doherty *et al.*[69] 2002 *Country:* Bangladesh *Study design:* double-blind RCT *Setting:* secondary care *Number of centres:* one *Funding:* Nestlé UK and the Department of Child Life and Health, University of Edinburgh. Ciba-Geigy, Bangladesh, provided zinc suspensions	*Intervention one:* 1.5 mg zinc/kg body weight for 15 days followed by placebo for 15 days *Intervention two:* 6.0 mg zinc/kg body weight for 15 days followed by placebo for 15 days *Intervention three:* 6.0 mg zinc/kg body weight for 30 days Elemental zinc was provided as zinc sulphate in all groups. Mothers were instructed how to administer the supplements using labelled syringes, which they continued to use at home up to day 30 *Other interventions used:* on recruitment, all were treated identically with broad-spectrum antibiotics, diarrhoea and skin sepsis was treated if present. All received a liquid diet with gradually increasing energy and protein according to malnutrition type, vitamin A and a daily multivitamin supplement. Full details in separate table. Days 1–15 involved intensive inpatient nutritional rehabilitation and health education (no details of the latter provided). Subjects discharged on day 15 if clinically fit and followed as outpatients	*Definition of SAM:* not explicitly stated, but presumed the same as the inclusion criteria, i.e. W/A < 60% of NCHS median for age, had nutritional oedema, or both *Number of participants: N* = 141 [intervention one (1.5 mg zinc/placebo) *n* = 49; intervention two (6 mg zinc/placebo) *n* = 49; intervention three (6 mg zinc/6 mg zinc) *n* = 43] *Sample attrition/dropout:* 106 (75%) completed; *n* = 16 (11%) dropouts (six because caregiver discharged them, 10 lost to follow-up); 19 (13.5%) deaths. *Dropouts by group:* 1.5 mg zinc/placebo *n* = 4; 6.0 mg zinc/placebo: *n* = 3; 6.0 mg zinc/6.0 mg zinc *n* = 9 *Sample crossovers:* none *Inclusion criteria:* aged 6–36 months and were W/A < 60% of NCHS median for age, had nutritional oedema, or both. Clinically stabilised within 1 week of admission and able to tolerate oral nutritional rehabilitation. Caregivers agreed that their child would remain in hospital for a further 15 days, and be followed up for a total of 90 days *Exclusion criteria:* strong suspicion of underlying TB (contact history and history of prolonged temperature elevation or cough) *General characteristics of participants:* severely malnourished children living within 2-hour travelling distance of hospital. 57% were aged < 1 year and average WHZ was –2.66	*Primary outcomes:* not explicitly stated *Outcomes included:* mortality (during inpatient and outpatient phases) and changes in anthropometric variables (*z*-scores, knemometry, skinfold thickness, MUAC) The linked paper[69] reports on insulin-like growth factor-1, its binding proteins, bone formation and collagen turnover. No further information relating to these outcomes has been data extracted *Method of assessing outcomes*: weight and length were measured by a team of four nurses and four nutritionists who had received an 8-week training course Two observers undertook all of the knemometry (distance between knee and heel), skinfold and MUAC measurements after an 8-week training period. Five knemometric readings were taken at each assessment and the mean was accepted unless the SD was > 1 mm All staff involved in anthropometric data gathering were subject to regular, unscheduled, formal assessments of measurement technique Weight – electronic scale, graduations to 20 g Length – rollameter with graduations to 1 mm. All measurements taken with child supine Skin-fold thickness – calipers graduated to 0.2 mm MUAC – standard non-stretch tape measure with graduations to 1 mm All anthropometric variables were based on NCHS medians

During in patient phase: body weight recorded daily, knemometry on alternate days, all other anthropometric variables on days 1, 8 and 15

During follow-up: all nutritional measurements recorded together in the morning

Adverse symptoms: none reported

Length of follow-up: during inpatient phase (15 days), and subsequently as outpatients on days 21, 30, 45, 60, 75 and 90

Recruitment dates: November 1995 to November 1996

Characteristics of participants:

Characteristic	Intervention one (1.5 mg zinc/ placebo) ($n=49$)	Intervention two (6 mg zinc/placebo) ($n=49$)	Intervention three (6 mg zinc/6 mg zinc) ($n=43$)
Age, months	15.5 ± 8.7	15.0 ± 9.0	16.3 ± 8.6
WAZ	–4.47 ± 0.91	–4.56 ± 0.98	–4.66 ± 0.86
WHZ	–2.56 ± 0.97	–2.73 ± 0.90	–2.71 ± 0.93
HAZ	–3.89 ± 1.3	–3.79 ± 1.4	–3.98 ± 1.45
Malnutrition, *n*			
Marasmus	29	27	26
Marasmic kwashiorkor	15	14	11
Kwashiorkor	5	7	6
Time from admission to recruitment, days	2.5 ± 1.5	3.5 ± 2.2	2.7 ± 1.8
Lower leg length, cm	17.08 ± 2.30	16.91 ± 2.23	17.31 ± 2.24

Comments: data presented are mean ± SD unless otherwise stated

57% of participants were < 1 year of age. Participants were both severely wasted and severely stunted

Results

Outcomes	Intervention one (1.5 mg zinc/ placebo) ($n=49$)	Intervention two (6 mg zinc/placebo) ($n=49$)	Intervention three (6 mg zinc/6 mg zinc) ($n=43$)
Inpatient death, *n*	2	5	6
Outpatient death, *n*	0	3	3
Self-discharge or loss to follow-up, *n*	4	3	9

Comments: there were more deaths in the groups receiving 6.0 mg zinc/kg as inpatients. This trend was identified at the interim analysis of the first 100 subjects and enrolment was suspended after 141 recruits. When supplementation regimens two and three were combined, the risk of death was significant ($p=0.03$) with exposure to 6.0 mg zinc/kg as compared with 1.5 mg zinc/kg initially (Yates-corrected chi-squared value of risk of death at RR 4.52, 95% CI 1.09 to 18.8). Clinician's impression was that cause of death was sepsis in most cases, and 13 of the 18 deaths occurred when children were inpatients. The paper presents an analysis looking for possible predictors/prognostic factors for death, but none of the factors considered (age, degree of wasting and stunting, severity of initial illness, type of malnutrition) were found to predict death in association with exposure to the higher initial dose of zinc (data not extracted here)

Change in anthropometric outcomes over 90 days	Intervention one (1.5 mg zinc/placebo) ($n=43$)	Intervention two (6 mg zinc/ placebo) ($n=38$)	Intervention three (6 mg zinc/6 mg zinc) ($n=25$)	95% CI for mean difference
WAZ	1.35 ± 0.69	1.51 ± 0.65	1.45 ± 0.66	Intervention two–intervention one: (–0.27 to 0.52)
				Intervention three–intervention two: (–0.47 to 0.38)
WHZ	1.54 ± 0.93	1.67 ± 0.78	1.62 ± 0.86	Intervention two–intervention one: (–0.14 to 0.46)
				Intervention three–intervention two: (–0.39 to 0.27)
HAZ	0.44 ± 0.32	0.48 ± 0.38	0.49 ± 0.27	Intervention two–intervention one: (–0.11 to 0.2)
				Intervention three–intervention two: (–0.17 to 0.18)
Lower leg length change (knemometry), cm	1.04 ± 0.48	1.03 ± 0.49	1.03 ± 0.33	Intervention two–intervention one: (–0.23 to 0.2)
				Intervention three–intervention two: (–0.22 to 0.22)
Skinfold thickness, mm	3.06 ± 1.94	3.63 ± 1.87	3.61 ± 1.86	Intervention two–intervention one: (–0.29 to 1.43)
				Intervention three–intervention two: (–0.97 to 0.94)
MUAC, cm	1.66 ± 1.40	1.98 ± 1.17	1.9 ± 1.38	Intervention two–intervention one: (–0.26 to 0.89)
				Intervention three–intervention two: (–0.72 to 0.57)

Comments: all values mean ± SD. No significant differences in change of any anthropometric variable between regimens

Good catch-up growth was achieved over 90 days with the average intragroup WHZ improved from 1.54 to 1.67 units, and the HAZ improved from 0.44 to 0.49 units. Lower leg length grew on average 1.03–1.04 cm in 90 days (data presented in figures, but not extracted)

Safety: in discussion the authors speculate that the detrimental effect of zinc seen in their study may have been because most children had intercurrent infections when micronutrient supplementation was started early in the treatment regimen. Other trials of zinc supplementation have administered zinc at a later stage of rehabilitation, a point when ongoing sepsis is much less likely, although this is unlikely to be representative of practice in most nutritional rehabilitation units

HIV: NR

Barriers to implementation

A general difficulty in this setting is the pressure on caregivers to leave hospital as quickly as possible. This is presumably why in this study, caregivers were required to consent to their child remaining in hospital for 15 days. Nevertheless, some caregivers still discharged their child early before completion of treatment

Methodological comments

Allocation to treatment groups: an independent observer performed stratified randomisation into three zinc supplementation regimens. Variable length blocks within six strata generated by age (< 13 months and 13–36 months) and type of malnutrition (as defined by Wellcome classification: marasmus; marasmic kwashiorkor and kwashiorkor) were used

Blinding: double-blind study. The zinc sulphate and placebo suspensions were indistinguishable and both were formulated and provided by Ciba-Geigy, Bangladesh. Bottles were identical and labelled sequentially from one to 300. On recruitment to the study, two bottle numbers were provided by the independent observer and the corresponding bottles were then selected for that patient [labelled as Bottle A for days 1–15 (either 1.5 or 6.0 mg zinc/kg), and Bottle B for days 16–30 (either 6.0 mg zinc/kg or placebo)]

Comparability of treatment groups: states that baseline characteristics were similar between the groups (no *p*-values reported). Also, numbers of children with kwashiorkor (10–15%), marasmic kwashiorkor (25–30%) and marasmus (55–60%) were equally distributed between the groups

Method of data analysis: not ITT analysis. Epi-Info (version 6) was used for data recording and generation of *z*-scores. All anthropometric data were entered twice with a validation performed between the two entry records and against the hard copy of the data at the end of the data-gathering period. Differences between groups were compared by using Student's *t*-tests or one-way analysis of variance for quantitative variables with approximately normal distributions. Mann–Whitney or Kruskal–Wallis tests were used for ordinal variables, long-rank test for length of breastfeeding, and chi-squared tests for categorised variables, with Yates' correction used for 2×2 tables. For outcomes after discharge, the three treatment groups were treated as ordinal, and trends were tested by using Pearson or Spearman correlations as appropriate. Analysis of covariance was used to test differences in quantitative outcomes between groups after adjustment for other factors. An interim analysis of growth and mortality was planned after the first 100 subjects had been studied. When this took place, a trend for more inpatient deaths was observed in the groups receiving 6 mg zinc/kg and recruitment was suspended

Sample size/power calculation: sample size was calculated with a requirement for 90% power at the 5% level for 11 anthropometric and biochemical outcome variables, and a sample size of 60 was chosen, which was at the upper end of the calculated sample sizes. Although not explicitly stated, it appears that 60 should have been the sample size for each group; however, recruitment was suspended when 141 children had been enrolled, therefore the overall sample size of 180 was not reached. The authors of the paper do not comment on this

Attrition/dropout: reported for each group with reasons provided for the whole sample (not by group). A follow-up worker visited each dwelling at least twice after a subject defaulted from follow-up. All defaulters could not be found

General comments

Generalisability: no children < 6 months or > 36 months were included. It is not clear what proportion of the children would have met the current WHO criteria for SAM based on W/H (average initial *z*-score –2.66), and baseline data on MUAC were not presented. However, the majority of the sample were classified as having marasmus, which may suggest most participants would meet current criteria for SAM

Outcome measures: appropriate outcome measures were reported, together with information about data collection and methods for ensuring data quality

Intercentre variability: not applicable

Conflict of interest: NR

Standardised clinical management protocol: for all participants

For all if not already receiving them	Broad-spectrum antibiotics, usually ampicillin and gentamicin	
For those with a history of invasive diarrhoea	Nalidixic acid or mecillinam	
For those with skin sepsis	Cloxacillin	
Liquid dietary regimen according to type of malnutrition and whether diarrhoea present or not, and number of days since recruitment		
Per 100ml	No diarrhoea	Diarrhoea present
Type	Dried skim-milk based	Rice based
Energy	264 kJ	259 kJ
Protein	2.2 g	1.1 g
Zinc	0.3 mg	0.3 mg
Volume delivered every 2 hours (by nasogastric tube initially until appetite improved and child able to take full volume offered by mouth)	Oedematous malnutrition: 80 ml/kg/day Non-oedematous malnutrition 120 ml/kg/day With incremental steps up to 200 ml/kg/day during the inpatient stay of each child	
Breastfeeding was encouraged and solid food was offered ad libitum (no details of solid food provided)		
For those aged > 1 year	Vitamin A at admission 200,000 IU retinyl palmitate (60,000 µg retinol equivalent)	
For those aged < 1 year	Vitamin A at admission 100,000 IU retinyl palmitate (30,000 µg retinol equivalent)	
For all those recruited	Daily multivitamin supplement: 3000 IU vitamin A; 30 mg vitamin C; 600 IU vitamin D; 0.96 mg thiamine; 0.6 mg riboflavin; 0.6 mg pyridoxine; 0.6 mg nicotinamide	
If blood film taken on day 30 of the trial indicated iron deficiency anaemia	Iron supplementation (no details of dose provided)	

HAZ, weight-for-age *z*-score; IU, international units; NR, not reported; WAZ, weight-for-age *z*-score; WHZ, weight-for-height *z*-score.

Quality assessment for primary studies (modified for severe malnutrition)

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely ✓	Not likely	Cannot tell	
2. What percentage of selected individuals participated?	80–100% ✓	60–79%	< 60%	N/A	Cannot tell
Summary of selection bias	*Strong*	*Moderate*	*Weak*		
(Methodological strength of study)		✓			
B. Study design					
1. What was the study design?	RCT				✓
(Please tick appropriate and specify design if categorise as 'Other')	CCT				
	Cohort analytic (two group pre + post)				
	Case–control				
	Cohort [one group pre + post (before and after)]				
	Interrupted time series				
	Other – *specify*				
	Cannot Tell				
2. Was the study described as randomised?	Yes ✓	No			
If answer to no. 2 is 'no' complete summary then go to section C. Confounders. If answer is 'yes', answer no. 3 and no. 4 below, before completing summary for this section					
3. If answer was yes, was the method of randomisation described?	Yes ✓	No			
4. If answer was yes, was the method appropriate?	Yes ✓	No			
Summary of study design	*Strong*	*Moderate*	*Weak*		
(Methodological strength of study)	✓				
C. Confounders					
1. Were there important differences between groups prior to the intervention?	Yes	No ✓	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled [either in the design (e.g. by stratification or matching) or in the analysis]?	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders	*Strong*	*Moderate*	*Weak*		
(Methodological strength of study)	✓				
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No ✓	Cannot tell		
2. Were the study participants aware of the research question?	Yes	No ✓	Cannot tell		
Summary of blinding	*Strong*	*Moderate*	*Weak*		
(Methodological strength of study)	✓				

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes ✓	No	Cannot tell		
2. Were data collection tools shown to be reliable?	Yes ✓	No	Cannot tell		
Summary of data collection *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes ✓	No	Cannot tell		
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100% ✓	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100% ✓	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	Cannot tell ✓		
3. Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?	Yes	No	Cannot tell ✓		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
3. Are the statistical methods appropriate for the study design?	Yes ✓	No	Cannot tell		
4. Is the analysis performed by intervention allocation status (i.e. ITT) rather than actual intervention received?	Yes	No ✓	Cannot tell		
Global rating for study[a] (Overall methodological strength of study – based on sections A–F)	Strong ✓	Moderate	Weak		

HAZ, weight-for-age *z*-score; N/A, not applicable; ; WAZ, weight-for-age *z*-score; WHZ, weight-for-height *z*-score.
a Strong = four strong ratings with no weak ratings; moderate = one weak rating; weak = two or more weak ratings.

Gatheru *et al.* 1988[70]

Data extraction table

Reference and design	Intervention	Participants	Outcome measures
Author: Gatheru *et al.*[70] *Year:* 1988 *Country:* Kenya *Study design:* CCT *Setting:* inpatient *Number of centres:* one *Funding:* partly supported by the Kenya Medical Research Institute and the Ministry of Health	*Intervention:* zinc supplement of 5 mg elemental zinc/kg body weight/day given in three divided doses *Control:* no zinc The study also included a third group of children without kwashiorkor who are NR on here *Other interventions used:* both groups managed with high protein diet, motherly care and warmth. Breastfeeding continued if it was occurring. Antibiotics given if infection suspected or confirmed	*Definition of SAM:* kwashiorkor as defined by Wellcome classification *Number of participants:* $N = 82$ (zinc group, $n = 42$; control group, $n = 40$) *Sample attrition/dropout:* 24 participants did not complete the study, 11 in the zinc group and 13 in the control group *Sample crossovers:* none *Inclusion criteria:* diagnosis of kwashiorkor (Wellcome classification), aged 1–3 years *Exclusion criteria:* transfusions required, serious disease-like TB or measles present, sickle cell disease, absconded before clinical cure, and if death occurred before completion of study *General characteristics of participants:* patients aged 1–3 years with kwashiorkor	*Primary outcomes:* not specifically stated *Outcomes included:* ■ weight ■ serum zinc ■ diarrhoea ■ anorexia ■ oedema ■ skin ulcerations *Method of assessing outcomes:* weights recorded using the Toledo machine model 1361 Sentinel (Toledo, OH, USA) on admission and daily thereafter until discharge Serum zinc determined for admission (or latest on second day) and again on 10th day of treatment from a clotted blood sample by the atomic absorption spectroscopy method. One senior technician made all measurements Signs and symptoms were obtained at admission and daily by the author. Diarrhoea was noted if a patient passed more than three loose stools in 24 hours. Anorexia was noted if the child showed no interest or will to eat or drink the feeds given. Improvement in anorexia was marked by willingness to feed. Skin ulcerations included raw, wet, oozy lesions regardless of the presence of scalding and/or skin dyspigmentation. Healing of lesions was noted as drying up and return of normal colour *Discharge criteria:* oedema had subsided, diarrhoea had stopped, weight gain on three consecutive readings *Adverse symptoms:* NR *Length of follow-up:* 10 days *Recruitment dates:* presumably the same as the period of study which was March to September 1985

Characteristics of participants

Characteristic	Zinc ($n = 42$)	Control ($n = 40$)	*p*-value
Weight, mean kg	8.2	7.8	NR
Weight 6–10 kg, *n*	37	38	NR
Weight > 10 kg, *n*	5	2	NR
Serum zinc, mean (SD) µmol/l	6.4 (1.36)	6.4 (1.36)	NR
Sex, M : F, *n*	20 : 22	23 : 17	NR
Age 12–14 months, *n*	35	35	NR
Age 25–36 months, *n*	7	5	NR

Comments: the majority (70/82, 85.4%) of the participants were < 2 years of age

The mean (range) serum zinc of the whole group of kwashiorkor patients was 6.4 µmol/l (4.0–12.9 µmol/l), this was statistically significantly lower ($p < 0.05$) to serum zinc values obtained from a group of children without kwashiorkor

Results

Outcomes	Zinc	Control	*p*-value
Total weight gain,[a] mean (SD) g	531 (277)	338[b] (235)	<0.05
Daily weight gain, mean g	67	47.3	NR
Serum zinc[c] after 10 days of treatment, mean change from baseline µmol/l	0.62	–0.06	<0.05
Diarrhoea[d] duration, mean days (SD)	3.62 (2.78)	10.8 (3.4)	<0.001
Anorexia[d] duration, mean days (SD)	6 (3.16)	10.3 (5.01)	<0.01
Oedema[e] duration, range in days	2–18	2–18	NR
Oedema[e] lost by end of day 7, %	77	55	NR
Days taken to lose oedema[e], mean (SD)	6.3 (4.6)	8.1 (4.4)	<0.05
Days taken for skin lesions[d] to heal, mean (SD)	7.9 (3.1)	11.1 (2.1)	<0.03
Duration of hospital stay, mean days	15.9	16.9	>0.05, NS

Safety: NR

HIV: NR

Barriers to implementation

NR

Methodological comments

Allocation to treatment groups: children assigned to two groups in alternating order at the time of admission

Blinding: not blinded, although not explicitly stated. Paper refers to a need for a study using a double-blind design

Comparability of treatment groups: a limited amount of information was provided about the treatment groups at baseline and this was not commented on by the study authors except to note that both groups contained about equal numbers of males and females

Method of data analysis: to test the significance of differences observed in the results the conditional test for the mean using chi-squared approximation was used. A value of $p<0.05$ was accepted as significant. The analysis was not by ITT

Sample size/power calculation: none reported

Attrition/dropout: numbers reported for each group, but no reasons given

General comments

Generalisability: results likely to be applicable to other patients of this age (1–3 years) with kwashiorkor. The authors do not comment on whether the results could be extrapolated to different ages or patients with different forms of malnutrition (e.g. marasmus)

Outcome measures: appear appropriate. Mortality was not noted as an outcome, but as the paper states that those dying before completion of the study were excluded, it is presumed that some participants may have died

Intercentre variability: not applicable

Conflict of interest: not statement made

NR, not reported; NS, not statistically significant.

a Weight outcomes reported for $n=31$ of the zinc group and $n=27$ of the control group.

b Mean weight gain was reported differently in text (338 g) and table (383 g), it is not clear which value is the correct one.

c Numbers of participants contributing data to these outcomes is NR.

d Numbers of participants contributing data to these outcomes varied, and it is not known how many participants had diarrhoea, anorexia or skin lesions at baseline (zinc group: $n=17$ for diarrhoea, $n=26$ for anorexia and $n=10$ for skin lesion outcomes; Control group: $n=22$ for diarrhoea, $n=22$ for anorexia and $n=9$ for skin lesion outcomes).

e Oedema outcomes reported for $n=31$ of the zinc group and $n=26$ of the control group.

Quality assessment for primary studies (modified for severe malnutrition)

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely ✓	Not likely	Cannot tell	
2. What percentage of selected individuals participated?	80–100%	60–79%	< 60%	N/A	Cannot tell ✓
Summary of selection bias *(Methodological strength of study)*	*Strong*	*Moderate*	*Weak* ✓		
B. Study design					
1. What was the study design? (Please tick appropriate and specify design if categorise as 'Other')	RCT CCT ✓ Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted time series Other – *specify* Cannot Tell				
2. Was the study described as randomised?	Yes	No ✓			
If answer to no. 2 is 'no' complete summary then go to section C. Confounders. If answer is 'yes', answer no. 3 and no. 4 below, before completing summary for this section					
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*		
C. Confounders					
1. Were there important differences between groups prior to the intervention?	Yes	No	Cannot tell ✓		
2. If yes, indicate the percentage of relevant confounders that were controlled [either in the design (e.g. by stratification or matching) or in the analysis]?	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders *(Methodological strength of study)*	*Strong*	*Moderate*	*Weak* ✓		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes ✓	No	Cannot tell		
2. Were the study participants aware of the research question?	Yes ✓	No	Cannot tell		
Summary of blinding *(Methodological strength of study)*	*Strong*	*Moderate*	*Weak* ✓		

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes ✓	No	Cannot tell		
2. Were data collection tools shown to be reliable?	Yes	No	Cannot tell ✓		
Summary of data collection *(Methodological strength of study)*	*Strong*	*Moderate* ✓	*Weak*		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No ✓	Cannot tell		
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%	60–79% ✓	< 60%	Cannot tell	
Summary of withdrawals and dropouts *(Methodological strength of study)*	*Strong*	*Moderate* ✓	*Weak*		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100% ✓	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No	Cannot tell ✓		
3. Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?	Yes	No ✓	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
3. Are the statistical methods appropriate for the study design?	Yes ✓	No	Cannot tell		
4. Is the analysis performed by intervention allocation status (i.e. ITT) rather than actual intervention received?	Yes	No ✓	Cannot tell		
Global rating for study[a] (Overall methodological strength of study – based on sections A–F)	Strong	Moderate	Weak ✓		

N/A, not applicable.

a Strong = four strong ratings with no weak ratings; moderate = one weak rating; weak = two or more weak ratings.

Golden and Golden 1992[71]

Data extraction table

Reference and design	Intervention	Participants	Outcome measures
Author: Golden and Golden[71] *Year:* 1992 *Country:* not clearly stated but appears to be Jamaica, West Indies *Study design:* CCT *Setting:* inpatient *Number of centres:* one *Funding:* not explicitly stated but appears to be Medical Research Council and the Wellcome Trust	*Moderate Zinc:* basic diet supplemented with 76 µmol zinc/kg feed (equivalent to 5 mg zinc) *High Zinc:* basic diet supplemented with 153 µmol zinc/kg feed (equivalent to 10 mg zinc) *Low Zinc:* received basic diet throughout recovery (equivalent to 3.5 mg zinc) Zinc supplement a solution of zinc acetate containing 15.3 µmol (1 mg) zinc/ml *Other interventions used:* prior to selection children had been treated with antibiotics and antihelminthics as appropriate. They had been fed according to a standard protocol (details at end of table) After selection all received a high-energy soy-based formula (details at end of table)	*Definition of SAM:* Wellcome criteria *Number of participants:* $N=11$ (moderate zinc, $n=4$; high zinc, $n=3$; low zinc, $n=4$) *Sample attrition/dropout:* NR *Sample crossovers:* NR *Inclusion criteria:* within 2 weeks of admission, free of oedema and signs of systemic infection, ready to commence high-energy feeds *Exclusion criteria:* NR *General characteristics of participants:* all boys	*Primary outcomes:* no primary outcome explicitly stated *Outcomes included:* ■ dietary intake ■ weight gain ■ outcomes from balance studies reported, but not data extracted *Method of assessing outcomes:* daily dietary intakes calculated from the sum of the weight of formula taken at the eight daily feeds Body weights measured to nearest gram at 0800 hours each day. Minimum weight was taken as 0% recovery, 100% recovery was defined as the weight of a reference child (NCHS) of same length as the patient at the time of minimum weight measurement Metabolic balance studies were performed, but details of these not data extracted *Adverse symptoms:* not explicitly reported (although diarrhoea occurred during 9 of 32 balance experiments) *Length of follow-up:* not stated, but outcomes reported here are for 6-week follow-up *Recruitment dates:* NR

Characteristics of participants

Characteristic	Low zinc ($n=4$)	Moderate zinc ($n=4$)	High zinc ($n=3$)	*p*-value
Age, months	18 ± 4	15 ± 2	13 ± 4	NR
Plasma zinc, µmol	9.6 ± 1.9	11.1 ± 1.4	9.9 ± 1.3	NR
Weight, kg	4.9 ± 0.3	5.1 ± 0.4	4.9 ± 0.8	NR
Length, cm	67 ± 1	70 ± 2	68 ± 4	NR
L/A %	82 ± 3	88 ± 3	90 ± 1	NR
W/L %	63 ± 2	60 ± 4	61 ± 2	NR

Comments: baseline data reported as mean ± SEM

Overall age range 6–31 months (median 15 months). Before selection to the trial, nine children had marasmic kwashiorkor and two had marasmus

L/A % and W/L % are per cent of NCHS reference values

Results

Outcomes during first 6 weeks of recovery	Low zinc ($n=4$)	Moderate zinc ($n=4$)	High zinc ($n=3$)	*p*-value
Energy intake, kJ/kg/day	705 ± 18	730 ± 26	701 ± 35	NR but states not significantly different for either measure
Nitrogen intake mmol/kg/day	41 ± 3	42 ± 4	42 ± 3	
Rate of weight gain, g/kg/day	10.10 ± 0.22	11.60 ± 0.95	11.67 ± 1.41	No significant difference, *p*-value NR
Energy cost of tissue deposition, kJ/g	29.3 ± 2.6	24.8 ± 1.7	25.0 ± 0.6	NR

Comments: values are mean ± SEM

Although zinc-supplemented children gained weight faster, difference with low-zinc group was NS. Energy cost of tissue deposition (ECTD) values higher in the low-zinc group, no *p*-value reported and states will be published separately

Outcomes from metabolic balance studies not data extracted

Safety: NR

HIV: NR

Barriers to implementation

NR

Methodological comments

Allocation to treatment groups: selected within 2 weeks of admission. Consecutive children assigned first to moderate-zinc group, then to low-zinc group, then to high-zinc group

Blinding: NR

Comparability of treatment groups: states that at selection there were no significant anthropometric differences among the groups, and plasma zinc was also not different among the zinc groups

Method of data analysis: data were analysed using the statistical routines in Systat (Systat Software Inc., Evanston, IL, USA). ANOVA with post-analysis contrasts and repeated measures analysis of variance were used to assess differences in results. Statistical significance was assumed at the 5% level. The results were presented as means ± SEM, and in some cases as individual values

Sample size/power calculation: none reported

Attrition/dropout: NR, appears to be none

General comments

Generalisability: participants were all boys (presumably to facilitate separate collection of urine and faeces during metabolic balance experiments); however, there does not seem to be any reason why the results would not hold for girls also

Outcome measures: appear appropriate, but the method of obtaining weights and lengths was NR

Intercentre variability: not applicable

Conflict of interest: no statement made. Funding appears to come from the Medical Research Council and the Wellcome Trust

Initial feeding protocol (before selection into trial)

Cow's milk diet:

- 0.4 MJ/child/day
- 0.6 g protein/kg/child/day

Supplemented with:

- potassium 4 mmol/kg/child/day
- magnesium 1 mmol/kg/child/day
- vitamins Tropivite 1 ml/day (contains A, B1, B2, C and nicotinamide)
- folic acid 5 mg/day

None received oral or topical zinc prior to selection

High-energy feeding protocol (after entry into trial)

Sobee, Mead Johnson diet (Mead Johnson and Company, Evansville, IN, USA):

- 133 g/kg, supplemented with arachis oil 59 g/kg, and sucrose 50 g/kg

Contents per kg feed:

- 5.6 MJ
- 29 g protein
- 1.33 mmol phytic acid
- 54 µmol zinc

Fed by cup 3-hourly, to appetite (notes that this usually increased rapidly)

Potassium, magnesium and vitamin supplements continued as previous dosage

Ferrous sulphate commenced 0.4 mmol/child/day

ANOVA, analysis of variance; ECTD, energy cost of tissue deposition; L/A, length-for-age; NR, not reported; NS, not statistically significant; SEM, standard error of the mean.

Quality assessment for primary studies (modified for severe malnutrition)

A. Selection bias

1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely ✓	Not likely	Cannot tell	
2. What percentage of selected individuals participated?	80–100%	60–79%	< 60%	N/A	Cannot tell ✓
Summary of selection bias *(Methodological strength of study)*	*Strong*	*Moderate*	*Weak* ✓		

B. Study design

1. What was the study design? (Please tick appropriate and specify design if categorise as 'Other')	RCT				
	CCT				✓
	Cohort analytic (two group pre + post)				
	Case–control				
	Cohort [one group pre + post (before and after)]				
	Interrupted time series				
	Other – *specify*				
	Cannot Tell				
2. Was the study described as randomised?	Yes	No ✓			

If answer to no. 2 is 'no' complete summary then go to section C. Confounders. If answer is 'yes', answer no. 3 and no. 4 below, before completing summary for this section

3. If answer was yes, was the method of randomisation described?	Yes	No		
4. If answer was yes, was the method appropriate?	Yes	No		
Summary of study design *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*	

C. Confounders

1. Were there important differences between groups prior to the intervention?	Yes	No ✓	Cannot tell	
2. If yes, indicate the percentage of relevant confounders that were controlled [either in the design (e.g. by stratification or matching) or in the analysis]?	80–100%	60–79%	< 60%	Cannot tell
Summary of confounders *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*	

D. Blinding

1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Cannot tell ✓	
2. Were the study participants aware of the research question?	Yes	No	Cannot tell ✓	
Summary of blinding *(Methodological strength of study)*	*Strong*	*Moderate*	*Weak* ✓	

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes	No	Cannot tell ✓		
2. Were data collection tools shown to be reliable?	Yes	No	Cannot tell ✓		
Summary of data collection *(Methodological strength of study)*	*Strong*	*Moderate*	*Weak* ✓		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No ✓	Cannot tell		
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100% ✓	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100% ✓	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes ✓	No	Cannot tell		
3. Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?	Yes	No ✓	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
3. Are the statistical methods appropriate for the study design?	Yes ✓	No	Cannot tell		
4. Is the analysis performed by intervention allocation status (i.e. ITT) rather than actual intervention received?	Yes ✓	No	Cannot tell		
Global rating for study[a] (Overall methodological strength of study – based on sections A–F)	Strong	Moderate	Weak ✓		

N/A, not applicable.
a Strong = four strong ratings with no weak ratings; moderate = one weak rating; weak = two or more weak ratings.

Hemalatha *et al.* 1993[72]

Data extraction table

Reference and design	Intervention	Participants	Outcome measures
Author: Hemalatha *et al.*[72] *Year:* 1993 *Country:* India *Study design:* CCT (after quality assessment) *Setting:* inpatient *Number of centres:* one *Funding:* NR	*Intervention:* zinc as zinc sulphate ($zincSO_4$) in a capsule (40 mg elemental zinc per capsule). Single dose each day. Estimated to be about 6 mg/kg body weight/day *Control:* placebo capsule, one each day zinc and placebo administered from admission for 21 days *Other interventions used:* all children received a cereal-based diet and dairy milk provided ad libitum. Details in separate table at end IM injection of vitamin A 100,000 IU	*Definition of SAM:* [v]Gómez classification with W/A < 60% of that expected (NCHS standard). Those with loss of subcutaneous fat and with muscle wasting (marasus), those with oedema with wasting (marasmic kwashiorkor) *Number of participants:* $N = 33$ (zinc $n = 16$, placebo $n = 17$) *Sample attrition/dropout:* NR (but there is missing data) *Sample crossovers:* none *Inclusion criteria:* children hospitalised for rehabilitation from severe PEM *Exclusion criteria:* clinical evidence of any infection *General characteristics of participants:* children aged 1–5 years in hospital with SAM	*Primary outcomes:* none specifically reported *Outcomes included:* ■ time taken for oedema to resolve ■ weight change ■ duration of morbidity because of infections ■ biochemical measures (haemoglobin, serum albumin, plasma copper, plasma and leucocyte zinc) *Method of assessing outcomes:* ■ food intake assessed by 24-hour dietary records ■ biochemical measures obtained from blood sample collected after overnight fast. Full details of methods used not extracted. Repeat measures at 4 weeks only possible in 25 children (remainder unwilling to provide sample) ■ zinc content of three random 1-day diet samples were analysed *Adverse symptoms*: NR *Length of follow-up:* 1 month *Recruitment dates:* August 1990 to August 1991

Characteristics of participants

Characteristic	Zinc ($n = 16$)	Placebo ($n = 17$)	*p*-value
Age (years)			
1–2	6		NR
2–5	27		
Marasmic kwashiorkor, *n* and mean weight (SD)	$n = 7$, 7.5 kg (0.56)	$n = 7$, 7.3 kg (0.49)	NR
Marasmic. *n* and mean weight (SD)	$n = 9$, 6.7 kg (0.56)	$n = 10$, 7.2 kg (0.38)	NR
Leucocyte zinc µg/10^{10} cells, *n* and mean weight (SD)	$n = 12$, 46.9 (5.490)	$n = 10$, 45.7 (4.409)	NR
Plasma zinc µg/dl, *n* and mean weight (SD)	$n = 13$, 80.4 (9.972)	$n = 12$, 83.6 (10.363)	NR, but stated they were comparable at baseline
Plasma copper µg/dl, *n* and mean weight (SD)	$n = 13$, 112.1 (9.487)	$n = 12$, 99.1 (15.346)	NR, but stated they were comparable at baseline

Comments: initial zinc and copper status of the zinc group and placebo group described as comparable, and statistically significantly lower ($p < 0.001$) than levels in healthy children (not data extracted). Few details about baseline characteristics presented

Results

Primary outcomes	Zinc ($n=16$)	Placebo ($n=17$)	*p*-value
Leucocyte zinc µg/10^{10} cells, *n* and mean (SE)	$n=12$,[a] 107.2 (13.224)	$n=10$, 70.9 (8.414)	NR
Leucocyte zinc, change from baseline[b] µg/10^{10} cells	$n=12$[a] 60.3 $p<0.001$	$n=10$ 25.2 $p<0.025$	
Plasma zinc, µg/dl, mean (SE)	$n=13$, 107.5 (11.822)	$n=12$, 68.2 (7.031)	NR
Plasma zinc, change from baseline,[b] µg/dl	$n=13$ 27.1 $p<0.01$	$n=12$ –15.4 $p=$NS	
Plasma copper µg/dl, *n* and mean (SE)	$n=13$ 145.3 (8.621)	$n=12$ 144.8 (13.258)	NR
Plasma copper, change from baseline,[b] µg/dl	$n=13$ 33.2 $p<0.01$	$n=12$ 45.7 $p=0.025$	
Days for oedema to disappear, mean (SE)	9.0 (2.035)	15.7 (2.7)	NS
Duration of morbidity, days, mean (SE)	6.3 (0.959)	7.7 (1.040)	c
Weight gain g/kg body weight/day, *n* and mean weight (SE) in:			
Week one	$n=16$, 22.2 (8.365)	$n=16$, 31.1 (9.629)	NR
Week two	$n=15$, 25.1 (5.892)	$n=17$, 23.7 (7.494)	NR
Week three	$n=14$, 23.1 (4.945)	$n=16$, 22.3 (6.155)	NR
Week four	$n=12$, 22.6 (5.100)	$n=15$, 24.5 (5.035)	NS

Comments: data on haemoglobin and albumin levels are presented (again no between-group comparison), but have not been data extracted. Data on average energy intake in the two groups is provided separately for each of weeks 1 to 4 but these have not been data extracted

Overall reports that zinc supplementation did not have any additional benefit on the clinical or biochemical responses measured

Safety: NR other than a statement that the zinc supplements as given in the study were not found to adversely affect plasma copper levels

HIV: NR

Barriers to implementation

NR

Methodological comments

Allocation to treatment groups: no details provided. Only states that zinc capsule or placebo was randomly administered

Blinding: capsules coded in a laboratory by a person not connected with the study. After analysing clinical findings and completing the biochemical estimations, data were decoded and results analysed

Comparability of treatment groups: initial zinc and copper status described as comparable in the two groups, but statistically significantly lower ($p<0.001$) than healthy children (based on data from 34 health children with normal nutritional status tested as part of the study). Few baseline characteristics presented

Method of data analysis: states that as the results were similar in marasmic and marasmic kwashiorkor children, the findings were pooled for each group. Similarly, results for boys and girls were combined because no significant sex-related differences were observed. *t*-tests used to compare between groups for outcomes of body weight gain and energy intake, paired *t*-tests used to compare before and after outcomes within groups for some outcomes. No other information provided

Sample size/power calculation: NR

Attrition/dropout: NR. However, it is clear from the information provided about numbers of participants contributing data to the different outcomes that there is missing data. For data derived from blood samples (leucocyte zinc, plasma zinc, plasma copper), data is missing because only 25 (of the 33) participants allowed a second blood sample to be taken at 4 weeks. For other outcomes, e.g. duration of morbidity, weight gain, no explanation for missing data is provided

General comments

Generalisability: results likely to be generalisable to children > 1 year in age with PEM, providing they do not have infection

Outcome measures: appear appropriate but, in general, between group comparisons have not been reported

Intercentre variability: not applicable

Conflict of interest: none reported

Rehabilitation diet

Energy/day	700 kJ (8–10% derived from protein)
Protein/kg body weight/day	3–4 g
Multivitamin	One tablet
Ferrous sulphate	20 mg elemental iron in one capsule

Dietary analysis showed mean dietary zinc values of 7.3 ± 0.49 mg/1 day's diet. Although not explicitly stated it is assumed that this was the dietary content received by all participants, with those in the zinc group receiving additional zinc via the supplement

IU, international units; NR, not reported; NS, not statistically significant.

a It is not explicitly stated, but has been assumed by the reviewer that numbers of participants contributing outcome data to the outcomes of leucocyte zinc, plasma zinc and plasma copper are the same as those reported for the baseline values – baseline and post-treatment values only available for the 25 children who allowed a second blood sample to be taken after treatment at 4 weeks.

b Change from baseline values calculated by reviewer. The *p*-values reported are for the within-group comparison between baseline and follow-up. No comparisons between the groups are reported for leucocyte zinc, plasma zinc and plasma copper.

c States groups were comparable, but no *p*-value reported.

Quality assessment for primary studies (modified for severe malnutrition)

A. Selection bias

1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely ✓	Not likely	Cannot tell	
2. What percentage of selected individuals participated?	80–100%	60–79%	< 60%	N/A	Cannot tell ✓
Summary of selection bias	*Strong*	*Moderate*	*Weak*		
(Methodological strength of study)			✓		

B. Study design

1. What was the study design?	RCT				
(Please tick appropriate and specify design if categorise as 'Other')	CCT				✓
	Cohort analytic (two group pre + post)				
	Case–control				
	Cohort [one group pre + post (before and after)]				
	Interrupted time series				
	Other – *specify*				
	Cannot Tell				
2. Was the study described as randomised?	Yes ✓	No			

If answer to no. 2 is 'no' complete summary then go to section C. Confounders. If answer is 'yes', answer no. 3 and no. 4 below, before completing summary for this section

3. If answer was yes, was the method of randomisation described?	Yes	No ✓			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design	*Strong*	*Moderate*	*Weak*		
(Methodological strength of study)	✓				

C. Confounders

1. Were there important differences between groups prior to the intervention?	Yes	No	Cannot tell ✓		
2. If yes, indicate the percentage of relevant confounders that were controlled [either in the design (e.g. by stratification or matching) or in the analysis]?	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders	*Strong*	*Moderate*	*Weak*		
(Methodological strength of study)			✓		

D. Blinding

1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No ✓	Cannot tell		
2. Were the study participants aware of the research question?	Yes	No ✓	Cannot tell		
Summary of blinding	*Strong*	*Moderate*	*Weak*		
(Methodological strength of study)	✓				

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes ✓ – zinc		No ✓ – weight	Cannot tell	
2. Were data collection tools shown to be reliable?	Yes		No	Cannot tell ✓	
Summary of data collection *(Methodological strength of study)*	*Strong*		*Moderate* ✓ – zinc	*Weak* ✓ – weight	
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes		No ✓	Cannot tell	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100%		60–79%	< 60% ✓	Cannot tell
Summary of withdrawals and dropouts *(Methodological strength of study)*	*Strong*		*Moderate*	*Weak* ✓	
G. Intervention integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100% ✓		60–79%	< 60%	Cannot tell
2. Was the consistency of the intervention measured?	Yes		No	Cannot tell ✓	
3. Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?	Yes		No ✓	Cannot tell	
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
3. Are the statistical methods appropriate for the study design?	Yes		No	Cannot tell ✓	
4. Is the analysis performed by intervention allocation status (i.e. ITT) rather than actual intervention received?	Yes		No ✓	Cannot tell	
Global rating for study[a] (Overall methodological strength of study – based on sections A–F)	Strong		Moderate	Weak ✓	

N/A, not applicable.

a Strong = four strong ratings with no weak ratings; moderate = one weak rating; weak = two or more weak ratings.

Khanum *et al.* 1988[73]

Data extraction table

Reviewer: DM	Date: 6 September 2010	Version: 2	Checked by: DH
Reference and design	**Intervention**	**Participants**	**Outcome measures**
Author: Khanum *et al.*[73] *Year:* 1988 *Country:* Bangladesh *Study design:* CCT *Setting:* inpatient (Children's Nutrition Unit) *Number of centres:* one *Funding:* NR	*Intervention:* zinc supplement [10 mg zinc/kg/day as zinc sulphate ($zincSO_4$) for those weighing < 6 kg; 50 mg daily for those > 6 kg] given on the 15th hospital day for 3 weeks *Control:* standard care (no zinc supplement) *Other interventions used:* all children received milk feeds, rice-based solid foods ad libitum up to four times/day, and vitamins and iron supplementation (see end of table for further details) Infections had been treated before the administration of the intervention (15th hospital day)	*Definition of SAM:* Waterlow 1976.[101] All children with oedema and all those, with or without oedema, who were ≤ 60% W/H *Number of participants:* $N = 60$ (zinc supplemented, $n = 30$; control, $n = 30$) *Sample attrition/dropout:* NR *Sample crossovers:* NR *Inclusion criteria:* SAM children who had been admitted to the Children's Nutrition Unit *Exclusion criteria:* NR *General characteristics of participants:* ■ all children were classified clinically as either kwashiorkor or marasmic kwashiorkor ■ age range: 5–60 months ■ mean age: 29 months ■ both sexes were equally represented The prevalence of infections such as diarrhoea (80%), pneumonia (56%), and of other nutrient deficiencies such as xerophthalmia (76%) and anaemia (50%) was similar in both groups	*Primary outcomes:* not specifically stated *Outcomes:* ■ mean plasma zinc concentration ■ weight gain ■ W/H ■ W/A *Method of assessing outcomes:* nutritional status was assessed by W/A (Harvard standard) for < 1 year, and by W/H (Stuart and Stevenson 1959[25]) and presence or absence of oedema for > 1 year One ml of venous blood was drawn for measurement of plasma zinc and albumin on admission, on the 15th hospital day, and on discharge (36th hospital day) Plasma zinc concentration was estimated by atomic absorption spectrophotometry Weight, height and mid-arm circumference were measured on admission. Body weight was recorded at the same time each day, initially each morning, then weekly, by the same person. Height was measured weekly Dietary intakes were measured by weighting each plate of food and leftovers; any vomitus was recorded for each feed and the total daily intake calculated. The energy value of samples of the diet was estimated by bomb calorimetry, and energy intake was calculated for each week as the average intake/day divided by the average weight of the child during that week *Adverse symptoms:* NR *Length of follow-up:* 5 weeks total study time (2 weeks lead in, 3 weeks of treatment; no additional follow-up after treatment ceased) *Recruitment dates:* NR

Characteristics of participants

Characteristic	Zinc supplemented ($n=30$)	Control (non-supplemented) ($n=30$)	*p*-value
Age (months)			
5 –12	4	2	NR
12–24	6	8	NR
24–36	8	8	NR
36–48	6	8	NR
> 48	6	4	NR
Kwashiorkor, *n* (%)[a]	13 (43)	9 (30)	NR, NS

Results

Outcomes	Zinc supplemented ($n=30$)	Control (non-supplemented) ($n=30$)	*p*-value
Plasma zinc concentration (mmol/l)[b]			
On admission day	8.23 ± 0.7	7.90 ± 0.7	NR
15th day (zinc started)	7.88 ± 0.7	8.07 ± 0.5	NR
36th day (discharged)	18.53 ± 1.5	10.56 ± 0.9	< 0.001
Weekly weight gain (g/week)			
First week	600 ± 99.9	468 ± 81.7	NR
Second week	521 ± 75.4	330 ± 65.9	NR
Third week (zinc started)	580 ± 67.6	342 ± 86.5	< 0.05
Fourth week	403 ± 41.6	269 ± 47.1	< 0.05
Fifth week	462 ± 42.4	374 ± 48.9	NR
Mean weight gain rate > 10 g/kg/day	66%	33%	0.02
W/H[c]			
On admission day	70 ± 1.3	67 ± 1.3	NR
Eighth day	76 ± 1.4	72 ± 1.0	< 0.05
15th day (zinc started)	80 ± 1.4	75 ± 1.1	< 0.05
22nd day	87 ± 1.2	79 ± 1.3	< 0.001
29th day	91 ± 1.4	82 ± 1.4	< 0.001
36th day (discharged)	95 ± 1.2	86 ± 1.2	< 0.001
W/A[c]	($n=29$)	($n=28$)	
On admission day	50.3 ± 1.61	47.6 ± 1.60	NR
Eighth day	52.5 ± 1.44	49.9 ± 1.44	NR
15th day (zinc started)	58.1 ± 1.53	52.3 ± 1.60	< 0.05
22nd day	62.0 ± 1.57	55.2 ± 1.75	< 0.01
29th day	64.8 ± 1.58	57.1 ± 1.85	< 0.01
36th day (discharged)	68.1 ± 1.58	59.7 ± 1.77	< 0.001
Per cent of patients with W/H according to the Harvard standard on discharge (36th day), *n* (%)	($n=30$)	($n=30$)	
< 80	0 (0)	5 (16.7)	NR
80–90	7 (23.3)	18 (60.0)	NR
≥ 90	23 (76.6)	7 (23.3)	< 0.001

Comments: results were reported as mean ± sem

Reports no significant difference in energy intake between groups during the total treatment period. The authors also report that weight gain was the same in both sexes; an increase in appetite following zinc supplementation was not observed, and supplemental zinc did not increase energy intake (both groups had a mean energy intake of 200 kcal/kg/day)

Safety: NR

HIV: NR

Barriers to implementation

NR

Methodological comments

Allocation to treatment groups: children were randomly selected during recovery at the Children's Nutrition Unit and were alternately allocated to the treatment or the control group

Blinding: NR. Assumed patients, care providers nor outcome assessors were blinded

Comparability of treatment groups: the supplemented group contained more cases of kwashiorkor (13 out of 30) compared with the unsupplemented controls (9 out of 30), but the difference was not significant. The age distributions, the prevalence of infections and the H/A on admission was similar in both groups (*p*-values NR)

Method of data analysis: Student's *t*-test and chi-squared test were used for statistical interpretation of data. A *p*-value of < 0.05 was accepted as significant. ITT analysis for all outcomes except W/A

Sample size/power calculation: NR

Attrition/dropout: NR, but appear to be none

General comments

Generalisability: the authors refer to the paper by Waterlow (1976) to define SAM.[101] However, it is not clear which were the criteria considered. According to the reported W/H on admission data, on average, participants just meet the WHO criteria (W/H < 70%). All children were diagnosed either kwashiorkor or marasmic kwashiorkor. Participants also met the Gómez severe third-degree malnutrition on admission (W/A < 60%)

The age range was 5–60 months, although the majority of participants were 12–48 months

A subsection of the population admitted to the Children's Nutrition Unit was randomly selected during recovery from SAM

Outcome measures: the outcome measures were appropriate. However, the impact of the intervention on mortality nor its adverse effects were reported

Intercentre variability: not applicable

Conflict of interest: NR

Recovery diets

Aimed to achieve a calorie intake of 100–120 kcal/kg/day in the first week, and thereafter 150–200 kcal/kg/day with approximately 2.5 g protein/kg/day; consisted of dried skimmed milk reconstituted with oil and sugar (100 kcal/100 ml), initially given 2-hourly day and night. Given 90–100 ml/kg/day during the first week and increased gradually to 120–250 ml/kg/day in four to six feeds a day

Solid cooked meals were offered from the first week; some children refused it initially, but within a few days solid diets were taken

Solid diets

Rice pudding or Suji (68 kcal/100 g) at 0800 hours; rice + vegetable + meat (beef) mixture (100 kcal/100 g) at 1200 hours; rolls or chapatti (60 kcal/100 g) at 1500 hours and rice + dal (100 kcal/100 g) at 1800 hours

All children received supplements of vitamins (Pharmavit), oral iron [4 mg Fe/kg/day as iron sulphate ($FeSO_4$)] and vitamin A capsules (100,000–200,000 IU)

The zinc content of individual food items ranged from 1.5–7 p.p.m.

IU, international units; NR, not reported; NS, not statistically significant; p.p.m., parts per million; sem, standard error of the mean.

a Percentage calculated by the reviewer.

b Plasma zinc concentration of healthy controls are reported, but have not been data extracted.

c As a percentage of the Harvard reference.

Quality assessment for primary studies (modified for severe malnutrition)

A. Selection bias					
1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely ✓	Not likely	Cannot tell	
2. What percentage of selected individuals participated?	80–100% ✓	60–79%	< 60%	N/A	Cannot tell
Summary of selection bias *(Methodological strength of study)*	*Strong*	*Moderate* ✓	*Weak*		
B. Study design					
1. What was the study design? (Please tick appropriate and specify design if categorise as 'Other')	RCT CCT ✓ Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted time series Other – *specify* Cannot Tell				
2. Was the study described as randomised?	Yes	No ✓			
If answer to no. 2 is 'no' complete summary then go to section C. Confounders. If answer is 'yes', answer no. 3 and no. 4 below, before completing summary for this section					
3. If answer was yes, was the method of randomisation described?	Yes	No			
4. If answer was yes, was the method appropriate?	Yes	No			
Summary of study design *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*		
C. Confounders					
1. Were there important differences between groups prior to the intervention?	Yes	No ✓	Cannot tell		
2. If yes, indicate the percentage of relevant confounders that were controlled [either in the design (e.g. by stratification or matching) or in the analysis]?	80–100%	60–79%	< 60%	Cannot tell	
Summary of confounders *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*		
D. Blinding					
1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Cannot tell ✓		
2. Were the study participants aware of the research question?	Yes	No	Cannot tell ✓		
Summary of blinding *(Methodological strength of study)*	*Strong*	*Moderate*	*Weak* ✓		

E. Data collection methods				
1. Were data collection tools shown to be valid?	Yes	No	Cannot tell ✓	a
2. Were data collection tools shown to be reliable?	Yes ✓	No	Cannot tell ✓	
Summary of data collection *(Methodological strength of study)*	*Strong*	*Moderate* ✓	*Weak* ✓	b
F. Withdrawals and dropouts				
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No ✓	Cannot tell	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100% ✓	60–79%	<60%	Cannot tell
Summary of withdrawals and dropouts *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*	
G. Intervention integrity				
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100% ✓	60–79%	<60%	Cannot tell
2. Was the consistency of the intervention measured?	Yes ✓	No	Cannot tell	
3. Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?	Yes	No ✓	Cannot tell	
H. Analysis				
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
3. Are the statistical methods appropriate for the study design?	Yes ✓	No	Cannot tell		
4. Is the analysis performed by intervention allocation status (i.e. ITT) rather than actual intervention received?	Yes	No ✓	Cannot tell		
Global rating for study[c] (Overall methodological strength of study – based on sections A–F)	Strong	Moderate ✓	Weak ✓	d	

N/A, not applicable.
a 'Yes' for zinc status, 'cannot tell' for weight.
b 'Moderate' for zinc status, 'weak' for weight.
c Strong = four strong ratings with no weak ratings; moderate = one weak rating; weak = two or more weak ratings.
d 'Moderate' if scoring using zinc (which is related to weight gain), 'weak' if scoring using weight gain. As our primary outcome of interest is weight gain, overall score is 'weak'.

Makonnen *et al.* 2003[74,75]

Data extraction table

Reference and design	Intervention	Participants	Outcome measures
Author: Makonnen *et al.*[74] *Linked paper:* Makonnen *et al.*[75] (paper excluded on outcomes) *Year:* 2003 *Country:* South Africa *Study design:* described as prospective, double-blinded RCT, but judged as CCT in quality assessment *Setting:* inpatient and community *Number of centres:* one *Funding:* Central Research Fund of the University of Free State and Nestlé, South Africa	*Intervention:* standard management with zinc supplementation [10 mg/d of zinc as zinc sulphate ($zincSO_4$) suspension given in drop form from first day of admission] *Control:* standard management with placebo *Other interventions used:* all children received initial management to treat hypoglycaemia and hypothermia, dehydration, electrolyte imbalance, septic shock, infections and any other problems, including vitamin deficiencies and anaemia Both groups received the standard treatment regimen: formula diet or continued breastfeeding Health education was given to mothers and carers when child was ready for discharge (Further details are at the end of the table)	*Definition of SAM:* PEM as defined by the Wellcome Trust Working Party[102] (see *Generalisability* for further details) *Number of participants:* $N=300$ (zinc supplemented, $n=150$; control, $n=150$) *Sample attrition/dropout:* total 46/300 (15%) did not complete follow-up three (90 days) Zinc group: 12/150 (8%), of which eight died Control group: 34/150 (23%), of which 28 died *Sample crossovers:* NR *Inclusion criteria:* PEM as defined by the Wellcome classification; aged 6–60 months, > 80% of expected W/A with signs and symptoms of kwashiorkor *Exclusion criteria:* severe congenital abnormalities, other medical conditions such as congenital heart disease, Down's syndrome, cerebral palsy, or refusal to participate in the study *General characteristics of participants:* aged 6–60 months. Approximately half the population had HIV, > 25% suspected to have TB, ≈ 40–50% had diarrhoea, vomiting and fever	*Primary outcomes:* mortality, morbidity (including infections), length of hospital stay, anthropometry and biochemical assays (such as serum zinc levels reported in linked paper[75]) *Secondary outcomes:* weight gain and other clinical assessments (including oedema, diarrhoea, fever and other infections) *Definitions:* criteria for discharge from hospital: ■ W/A > 80% or progressive weight gain > 5 g/kg/day for 3 successive days ■ Fever: temperature > 38 ºC ■ Hypothermia: temperature < 35.5 ºC *Method of assessing outcomes:* all data collection and physical examinations were done by the same trained medical officer and anthropometric data were collected by the same nurses Weight was recorded on admission daily using a UNICEF scale to the nearest 100 g, with the child naked or minimum clothing and preferably taken at the same time of the day with the same scale Length was recorded for 6–18 months of age using a firm horizontal board with a fixed vertical headpiece and a sliding vertical foot apiece. In older children, height was taken in a standing position The mid-arm circumference for all age groups was measured (in cm) with a non-stretchable tape measure, with the arms hanging loosely to the side. The measure was passed around the circumference of the arm at the same horizontal level as for the measurement of triceps skin-fold thickness A clinical examination and blood tests were done on admission. Venous blood was obtained under fasting conditions for measurement of serum zinc by atomic absorption spectrometry using Fernandez and Kahn's method.[103] HIV test using enzyme-linked immunosorbent assay (ELISA), TB test using Mantoux read at 48 hours Follow-up assessments done at 30, 60 and 90 days post-discharge *Adverse symptoms:* NR *Length of follow-up:* mean hospital stay was 11–12 days and follow-up for 3 months post-discharge *Recruitment dates:* from 1 January 1999

Characteristics of participants

Characteristic	Zinc supplemented ($n=150$)	Control (non-zinc supplemented) ($n=150$)	p-value
Male, %	48.7	50.7	NR
Aged 12–23 months, %	41	52	NR
Morbidity, *n* (%)			
Poor appetite	89 (59.3)	70 (46.7)	NR
Swelling of body	95 (63.3)	78 (52.0)	NR
Diarrhoea	72 (48.0)	67 (44.7)	NR
Vomiting	77 (51.3)	83 (55.3)	NR
Cough	55 (36.7)	57 (38.0)	NR
Fever	82 (54.7)	59 (39.3)	NR
Loss of weight	118 (78.7)	114 (76.0)	NR
Oral lesions	125 (83.3)	121 (80.7)	NR
Per cent of expected W/A on admission, *n* (%)			
<60%	56 (37.3)	54 (36.0)	NR
60–80%	81 (54.0)	77 (51.3)	NR
>80% with oedema[a]	12 (8)	18 (12)	NR
>80% without oedema	1 (0.7)	1 (0.7)	NR
Mid-arm circumference lower than fifth percentile, *n* (%)	96 (90.6)	105 (87.5)	NR
Weight on admission, mean ± SD	7.2 ± 2.0	7.5 ± 2.4	NR
Height on admission, mean ± SD	72.2 ± 8.2	72.7 ± 8.6	NR
Mid-arm circumference, mean ± SD	11.8 ± 1.6	11.9 ± 1.8	NR
HIV+ve, %	44.7	52	NR
Serum zinc (μmol/l), mean ± SD[b]	6.23 ± 1.83	6.25 ± 1.74	NR; 95% CI for difference –0.43 to – 0.39

Comments: the percentage of children with weight >80% of expected weight on admission was 8.7% in the zinc group and 12.7% in the control group. These differences were not statistically significant. More than 98% of participants in both groups with PEM were admitted for the first time. The majority were <2 years of age

The number and percentage of participants from rural areas, orphans and breastfed for ≥12 months, as well as the past medical history of subjects and controls on admission were reported, but have not been data extracted

Results

Primary outcomes	Zinc supplemented ($n=150$)	Control (non-zinc supplemented) ($n=150$)	Difference (95% CI)
Discharged after hospitalisation, %	92.7	80[c]	NR
Death after hospitalisation, *n* (%)	7 (4.7)	26 (17.3)	NR[d]
Death after readmission, *n*	1	2	NR
Total deaths, *n* (%)[e]	8 (5.3)	28 (18.7)	NR
Morbidity on follow-up (90 days), *n* (%)	$n=138$, 85–95 days[f]	$n=116$, 83–95 days[f]	**95% CI for difference**
Diarrhoea	4 (2.9)	31 (36.7)	–32 to –15.0
Vomiting	1 (0.7)	8 (6.9)	–11.2 to –1.2
Fever	4 (2.9)	12 (10.3)	–13.8 to –1.1
Oedema	0 (0)	0 (0)	–2.0 to 1.2
Acute respiratory infections	4 (2.9)	45 (38.8)	–44.7 to –26.2
Skin infection	1 (0.7)	8 (6.9)	–11.2 to –1.2
Pallor	32 (23.2)	62 (53.4)	–41.3 to –18.4
Anthropometry on discharge	$n=139$	$n=120$	
W/A, *n* (%)			
<60%	44 (31.7)	30 (25)	–4.4 to 17.4
60–80%	78 (56.1)	74 (61.7)	NR
>80% without oedema[b]	17 (12.2)	16 (13.3)	NR
Mid-arm circumference percentiles lower than fifth percentile, *n* (%)	92 (92.9)	82 (85.4)	–1.3 to 16.1
Anthropometry on follow-up (90 days)	$n=138$	$n=116$	
W/A, *n* (%)			
<60%	5 (3.6%)	16 (13.8)	–17.2 to –3.1
60–80%	52 (37.7%)	67 (57.8)	NR
>80% without oedema	81 (58.7%)	33 (28.4)	NR[s]
Mid-arm circumference percentiles lower than fifth percentile, *n* (%)	66 (54.1)	81 (77.9)	–35.2 to –11.5
Length of hospital stay, mean ± SD	10.9 ± 3.9	11.7 ± 5.9	NR; not statistically significant
Serum zinc at 90 days follow-up (µmol/l), mean ± SD[h]	10.13 ± 2.93	7.84 ± 1.72	95% CI for difference 1.68 to 2.90

Comments: p-values were NR

Data were presented for morbidities during the first 3 weeks of hospitalisation (no morbidity, poor appetite, oedema, diarrhoea, vomiting, cough, fever, weight loss, and oral lesions). The paper reports a general trend for the zinc-supplemented group to recover more rapidly, though it is not true for all symptoms, nor were there any statistically significant differences over the first 3 weeks

Data also presented for morbidities at 30-day and 60-day follow-up, but these have not been data extracted

Although length was measured at discharge and every follow-up visit, these results were clearly inaccurate and therefore omitted

Results for biochemical assays (additional primary outcomes) were reported on linked paper,[75] from which only serum zinc at 90 days has been extracted

Gastroenteritis was an important diagnosis in both groups, but showed regression during hospitalisation (78% in both groups in first week, 30.4% and 37.4% in zinc and control groups in second week, respectively)

The authors mention further monitoring and evaluation being carried out for secondary outcomes, but results for these were NR

Safety: NR

HIV: six out of seven (85.7%) children in the zinc group and 15 out of 26 (57.7%) children in the control group, who died in the hospital before discharge, were diagnosed to be HIV+ve. All of them had clinical evidence of HIV-related disease. According to the authors, these data suggest that even if the contribution to the death rate caused by possible HIV disease is eliminated, significantly more children in the control group died during hospitalisation than in the supplemented group

TB: TB distribution and related findings for both groups were very similar and would not have been a confounding variable for differences in outcome

Barriers to implementation

NR

Methodological comments

Allocation to treatment groups: children were randomly assigned to one of two treatment regimens. Randomisation was stratified by sex, age and percentage of expected W/A. If children were > 80% of expected weight, but had all the clinical features of PEM (kwashiorkor), they were randomised according to the list for 60–80%. No details of the randomisation method used were provided

Blinding: double-blinded study. For the non-zinc group, placebo was presented in a similar bottle and colour with similar taste and smell, so that medical personnel and parents could not differentiate between the zinc sulphate and placebo. No details on whether or not outcome assessors were aware of groups

Comparability of treatment groups: the demography of the subjects and controls was similar. Reports that the zinc group might have had a more severe disease profile on admission as more children in this group presented with a history of oedema and fever (table 2), but opposite is shown in table 3. The distribution of symptoms, anthropometry and past medical history was quite similar and comparable in both groups. No *p*-values were reported

Method of data analysis: an ITT analysis was not performed. The two groups were compared with respect to the outcome measures using 95% CIs for the differences in percentages or means. Characteristics were summarised per group by frequencies and percentages (for categorical variables) and means, SDs, medians, minima and maxima (for numerical variables). Anthropometric analyses were done using Epi-Info. Arm circumferences were categorised into percentiles according to tables provided by Frisancho.[104] All other analyses were done using Statistical Analysis System software (SAS Institute Inc, Cary, NC). Duration of breastfeeding was analysed using survival analysis. To compare children within a treatment group who survived with those who died, 95% CI for differences in medians were calculated, because of small group size and skewed distribution

Sample size/power calculation: the decision to include 150 children in each group was derived after analysis of the data of a pilot study, which included 60 children with PEM and 60 similar children in the control group

Attrition/dropout: in the zinc group, 150 children were entered, of which four (2.7%) absconded and seven (4.7%) died before discharge. One child was readmitted after 5 days discharge from hospital and therefore not assessed at follow-up one (30 days), but the four children who absconded did attend the first follow-up visit. Therefore, 142 supplemented children were assessed at follow-up one. One of these was readmitted at follow-up one and subsequently died, leaving 141 at follow-up two (60 days). At follow-up three (90 days), three children could not be traced and 138 were assessed. In the control group, of the 150 children that entered, four (2.7%) absconded and 26 (17.3%) died before discharge. Three children were readmitted, of which one died and two were discharged. At follow-up one, 121 children were assessed. The four children who absconded did attend the first follow-up visit. One child was readmitted and died. One did not turn up for assessment. One hundred and nineteen children were assessed at follow-up two. At follow-up three, three children could not be traced and 116 were assessed

In the two groups, the percentage of children who absconded was similar (2.7%). These eight children were all traced, attended the first follow-up, and it was decided to keep them in the study and their data analysed with the rest

General comments:

Generalisability: malnutrition is defined according to the Wellcome classification as a reduction in the expected body weight < 80% (of the Boston 50th percentile). Between 60% and 80% of expected weight is underweight in the absence of oedema, and kwashiorkor if oedema is present; < 60% of expected weight is marasmus in the absence of oedema, and marasmic kwashiorkor if oedema is present. It is not clear whether or not participants meet the WHO criteria for SAM. The majority of participants had 60–80% W/A on admission using the Wellcome classification, and the majority had MUAC lower than fifth percentile

Outcome measures: outcome measures such as W/A, mortality and morbidity were appropriate. However, outcomes as weight gain and adverse effects of the intervention were NR

Intercentre variability: not applicable

Conflict of interest: NR

Initial treatment began with admission to the hospital and lasted for about 7 days. Its principal aims were to treat or prevent hypoglycaemia, hypothermia, dehydration and electrolyte imbalance; treat septic shock; start feeding the child; treat infections; identify and treat any other problems, including vitamin deficiencies and manage severe anaemia and heart failure	
RL (20 ml/kg/hour) was given intravenously for severe dehydration or septic shock	
Most dehydrated children of both groups received ORS through a nasogastric tube. Children were reassessed every hour and rehydration stopped when the child was clinically rehydrated. ORS was continued until diarrhoea stopped or decreased significantly	
Standard treatment regimen: the treatment of the intervention and control groups was identical, with the exception of the addition of zinc in the management of the supplemented group. To avoid overloading of the intestine, liver and kidneys, small frequent amounts of food were given (50–100 ml every 4 hours). Children who were unable or unwilling to eat were fed by nasogastric tube as a temporary measure. Patients who did not require other emergency treatment (especially for dehydration or septic shock) were given formula diet (Disco-dried skimmed milk-sugar-oil mixture (DSM): 80 g DSM + 60 g oil + 50 g sugar + water up to 1000 ml) or continued breastfeeding in both the study and control group	
The rehabilitation phase began at about the second week of admission and lasted around 6 weeks. A child entered the rehabilitation phase when his/her appetite returned. The principal aims during this phase were to encourage the child to eat healthily, stimulate physical and emotional development and prepare the mother or caregivers to continue caring for the child after discharge	
Health education was given to mothers and carers on nutrition, care (e.g. feeding and nutrition), how to recognise the symptoms and signs of illness, when to seek medical assistance, home treatment for diarrhoea, fever and acute respiratory infections	
Children were followed up at the hospital at 30, 60 and 90 days after discharge. The aims of this stage were to increase feeding appropriately, monitor weight gain and mid-arm circumference, monitor the physical well-being and mental and emotional development of the child and determine their serum zinc levels	

NR, not reported.

a The clinical impression of kwashiorkor was confirmed in that all these children had an admission serum albumin < 30 g/l.

b Reported in linked paper;[74] median, minimum and maximum values were reported as well, but have not been data extracted.

c Reported as 80.7% in text but 120/150 = 80% according to study's Table 1.

d Significantly more children died by the end of hospitalisation in the control group than the zinc-supplemented group (reported as 95% CI 5.5 vs 19.5 in text, but not clear what this CI refers to).

e Calculated by the reviewer.

f Time elapsed from discharge to third follow-up.

g Reports in text that this difference is statistically significant but no *p*-value or CI is provided.

h Most children likely to have been discharged based on progressive weight gain of > 5 g/kg/day (rather than having W/A > 80%) as proportion with W/A > 80% on discharge is relatively small.

Quality assessment for primary studies (modified for severe malnutrition)

A. Selection bias

1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely ✓	Somewhat likely	Not likely	Cannot tell	
2. What percentage of selected individuals participated?	80–100% ✓	60–79%	< 60%	N/A	Cannot tell
Summary of selection bias	*Strong*	*Moderate*	*Weak*		
(Methodological strength of study)	✓				

B. Study design

1. What was the study design?	RCT			
(Please tick appropriate and specify design if categorise as 'Other')	CCT			✓
	Cohort analytic (two group pre + post)			
	Case–control			
	Cohort [one group pre + post (before and after)]			
	Interrupted time series			
	Other – *specify*			
	Cannot Tell			
2. Was the study described as randomised?	Yes ✓	No		

If answer to no. 2 is 'no' complete summary then go to section C. Confounders. If answer is 'yes', answer no. 3 and no. 4 below, before completing summary for this section

3. If answer was yes, was the method of randomisation described?	Yes	No ✓		
4. If answer was yes, was the method appropriate?	Yes	No		
Summary of study design	*Strong*	*Moderate*	*Weak*	
(Methodological strength of study)	✓			

C. Confounders

1. Were there important differences between groups prior to the intervention?	Yes	No	Cannot tell ✓	
2. If yes, indicate the percentage of relevant confounders that were controlled [either in the design (e.g. by stratification or matching) or in the analysis]?	80–100%	60–79%	< 60%	Cannot tell
Summary of confounders	*Strong*	*Moderate*	*Weak*	
(Methodological strength of study)			✓	

D. Blinding

1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No ✓	Cannot tell	
2. Were the study participants aware of the research question?	Yes	No ✓	Cannot tell	
Summary of blinding	*Strong*	*Moderate*	*Weak*	
(Methodological strength of study)	✓			

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes ✓	No	Cannot tell		
2. Were data collection tools shown to be reliable?	Yes	No ✓	Cannot tell		
Summary of data collection *(Methodological strength of study)*	*Strong*	*Moderate* ✓	*Weak*		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes ✓	No	Cannot tell		
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100% ✓	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100% ✓	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No ✓	Cannot tell		
3. Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?	Yes	No	Cannot tell ✓		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
3. Are the statistical methods appropriate for the study design?	Yes ✓	No	Cannot tell		
4. Is the analysis performed by intervention allocation status (i.e. ITT) rather than actual intervention received?	Yes	No ✓	Cannot tell		
Global rating for study[a] (Overall methodological strength of study – based on sections A–F)	Strong	Moderate ✓	Weak		

N/A, not applicable.

a Strong = four strong ratings with no weak ratings; moderate = one weak rating; weak = two or more weak ratings.

Schlesinger *et al*. 1992[76]

Data extraction table

Reference and design	Intervention	Participants	Outcome measures
Author: Schlesinger *et al.*[76] *Year:* 1992 *Country:* Chile *Study design:* double-blind CCT *Setting:* inpatient, tertiary care (closed nutritional recovery centre) *Number of centres:* one *Funding:* Nestlé Nutrition Research Grant Programme	*Intervention:* zinc-supplemented formula (zinc 15 mg/l), ad libitum, for 105 days *Control:* standard infant formula (zinc 3.2 mg/l), ad libitum, for 105 days Both formulas based on full-fat powered cow's milk fortified with vitamins and minerals as per standard infant formula (Nestlé, Switzerland) except for iron and zinc (see end of table for further details). The formulas differed only in zinc content, which was 3.2 mg/l in the standard formula. No other energy-containing supplements were given to either group *Other interventions used:* none reported	*Definition of SAM:* not specifically stated, but mean NCHS WAZ were < 3 SD on admission *Number of participants:* *N* = 39 (zinc supplemented, *n* = 19; control, *n* = 20) *Sample attrition/dropout:* none reported *Sample crossovers:* none *Inclusion criteria:* only reports marasmic infants with SAM *Exclusion criteria:* NR *General characteristics of participants:* SAM infants (< 1 year)	*Primary outcomes:* not specifically stated *Outcomes were:* ■ zinc status ■ trace element status ■ nutritional status (HAZ, WAZ and WHZ *z*-scores) ■ immune function *Method of assessing outcomes:* anthropometric measurements performed by a registered nurse on admission and at 15-day intervals. Intake was determined by weighing each bottle before and after feeding. Nude weights obtained before first morning feed with an infant scale (Condor, Santiago, Chile) with a 5-g precision, calibrated at regular intervals. Lengths to nearest 0.1 cm determined by standard procedures with a portable infantometer. Weight and length measurements assessed using NCHS growth percentile curves. *z*-scores calculated with the PCTL9Z Anthropometry Subroutine (US Centre for Health Promotion and Education, National Centre for Disease Control, Atlanta, GA, USA) Plasma and polymorphonuclear leucocyte zinc concentrations determined using atomic absorption spectrophotometry. Polymorphonuclear leucocytes were isolated by dextran sedimentation and Ficoll Hypaque-gradient centrifugation. Iron nutrition assessed on admission and after 60 and 105 days by haemoglobin with the cyanomethemoglobin method (Coulter Counter ZBI, FI, USA) and by serum ferritin with a radioimmunoassay (Travenol, Massachusetts). Serum copper concentrations determined by atomic absorption spectrophotometry on admission and after 30, 60 and 105 days Detailed methodology is reported for assessment of the immunological profile but is not extracted here Signs and symptoms of morbidity were recorded daily on a chart by the attending physician. Every infectious episode was analysed using: mean episodes/infant, mean duration days of each episode/infant, and mean per cent of infected days in the 105 days: [(number days with infection/ number observed days) × 100] *Adverse symptoms:* ■ upper and lower respiratory infection ■ otitis media ■ acute diarrhoeal episode (presence of liquid stools for > 12 hours) ■ skin and mucous candidiasis ■ purulent conjuctivitis *Length of follow-up:* nothing further than the 105 days of nutritional rehabilitation treatment *Recruitment dates:* NR

Characteristics of participants

Characteristic	Zinc-supplemented formula ($n=19$)	Control formula ($n=20$)	p-value
Sex, M:F	10:9	10:10	NS
Age, months	7.05 (2.0)	8.1 (3.0)	NS
WAZ on admission	–3.13 (0.71)	–3.21 (0.87)	NS
Birth weight, g	2886 (307)	3040 (268)	NS
Plasma zinc µmol/l, mean ± SD	19.4 ± 5.5 ($n=18$)	23.4 ± 8.4 ($n=17$)	NS
Serum copper µmol/l, mean ± SD	19.5± 7.0 ($n=18$)	20.1 ± 7.4 ($n=17$)	NS
Intakes/kg/day			
Energy, kJ	674 (105)	682 (80)	NS
Protein, g	4.4 (0.7)	4.5 (0.5)	NS
Zinc, mg	1.9 (0.3)	0.35 (0.04)	< 0.01[a]
Iron, mg	1.9 (0.3)	1.9 (0.2)	NS
Copper, mg	0.04 (0.007)	0.04 (0.005)	NS
Comments: values are mean (± SD) unless otherwise stated			
Outcomes	**Zinc-supplemented formula ($n=19$)**	**Control formula ($n=20$)**	***p*-value**
z-scores, mean (± SD)			
H/A			
On admission	–3.27 (0.93)	–3.19 (1.34)	NS
30 days	–3.02 (0.89)	–3.06 (1.04)	NS
60 days	–2.73 (0.95)	–2.78 (1.12)	NS
105 days	–2.64 (0.86)	–2.56 (0.84)	NS
W/A			
On admission	–3.13 (0.71)	–3.21 (0.87)	NS
30 days	–2.32 (0.62)	–2.36 (0.74)	NS
60 days	–2.04 (0.1)	–1.95 (0.91)	NS
105 days	–1.66 (0.64)	–1.59 (0.88)	NS
W/H			
On admission	–0.83 (0.6)	–1.18 (0.81)	NS
30 days	–0.07 (0.75)	–0.02 (1.15)	NS
60 days	0.12 (0.84)	0.17 (1.27)	NS
105 days	0.42 (0.81)	0.32 (1.22)	NS
Increase in L/A percentile score in relation to admission,% (n/N)			
30 days	58 (11/19)	20 (4/20)[b]	< 0.002
45 days	79 (15/19)	45 (9/20)[b]	< 0.03
Plasma zinc µmol/l, mean ± SD 105 days	18.6 ± 4.3 ($n=18$)	18.0 ± 5.8 ($n=17$)	NS
Serum copper µmol/l, mean ± SD 105 days	24.4 ± 4.4 ($n=18$)	22.8 ± 4.6 ($n=17$)	NS

Comments: plasma zinc and serum copper concentrations at 30 and 60 days have not been data extracted. There were no significant differences between the groups

Nutritional status:

- Data were further analysed by using the mean increment of L/A *z*-score at 0, 15, 30, 45, 60, 75, 90 and 105 days and presented in line graphs for the whole group and separately for males and females (but data not extracted here as graphs are not clear). The zinc group began to grow earlier than the control group, becoming significant after 30 days (*p*-value unreadable), whereas the increment for the control group started to be significant at day 45 ($p < 0.01$)
- Male infants in the zinc group grew significantly before control group males (*p*-value unreadable), but there was no difference in increment of HAZ in females

Other outcomes (micronutrients, immune function):

- Results are reported for trace element status (Hb, serum ferritin, anaemia, etc.) and immunocompetence, but these data are NR in relation to weight gain, *z*-score or mortality and therefore have not been data extracted
- A statistically significant difference was found in the proportion of participants defined as having a low plasma zinc and this favoured the zinc-supplemented group
- No statistically significant differences in leucocyte zinc were found between the groups

Safety:

- The number of otitis media episodes (mean ± SD) during the 105 days rehabilitation was 0.73 ± 0.9 vs 1.85 ± 2.3 for the zinc and control groups, respectively ($0.05 > p < 0.1$, Student's *t*-test)
- The number of acute diarrhoeal episodes was average two versus zero for the zinc and control groups, respectively. A statistically significant difference appeared when analysing the data using all three indices mentioned in *Method of assessing outcomes* (*p*-value NR). The diarrhoeal episodes lasted 1 or 2 days, exerting no impact on nutritional rehabilitation
- No differences were observed between groups in number or duration of upper and lower respiratory infection, purulent conjunctivitis, and skin and mucous candidiasis

HIV: NR

Barriers to implementation

NR

Methodological comments

Allocation to treatment groups: not a randomised study. No details regarding allocation of treatments

Blinding: states double blind, but no further details are given as to how blinding was ensured in the patients and care providers (formula was provided in bottles). No details whether or not outcome assessors were blinded

Comparability of treatment groups: few baseline characteristics were presented; reports there were no significant differences between groups nor between males and females (though no *p*-values reported)

Method of data analysis: appears to be ITT analysis for *z*-scores (full number of patients allocated to each treatment group were analysed). The Statistical Analysis System software (SAS Institute Inc., Cary, NC, USA) was used. The paired and non-paired *t*-test, Cochrane Mantel–Hanzel test, Fisher's exact probability test and stepwise logistic regression were used in the analysis of data. Significance was determined at $p < 0.05$

Sample size/power calculation: NR

Attrition/dropout: none reported

General comments

Generalisability: likely that most of the children would meet the current WHO criteria (mean WAZ < –3 SD). Unclear whether the children admitted to the tertiary centre were all those with SAM or a subsection. In addition, the mean age was 7–8 months on admission and, therefore, would not be generalisable to all children < 5 years

Outcome measures: outcomes were appropriate although mortality data not specifically reported (even though it appears to be zero)

Intercentre variability: N/A

Conflict of interest: funded by The Nestlé Nutrition Research Grant Program; no conflicts of interest are apparent

Composition of formula (per gram of powder)

Fat 0.26 g, protein 0.26 g, vitamin A 15.2 IU, cholecalciferol 3 IU, vitamin E 0.06 IU, vitamin C 1.5 mg, folic acid 0.45 µg, thiamine 3 µg, niacin 0.038 mg, vitamin B6 3 µg, biotin 0.11 mg, pantothenate 0.023 mg, riboflavin 4.5 µg, vitamin B12 0.011 µg, vitamin K 0.42 µg, choline 0.38 µg, inositol 0.23 mg, iodine 0.38 µg, copper 3.5 µg, iron 0.15 mg (as ferrous sulphate) and zinc 0.15 mg (as zinc chloride). Formula was prepared at 10% dilution

HAZ, weight-for-age *z*-score; IU, international units; L/A, length-for-age; NR, not reported; NS, not statistically significant; WAZ, weight-for-age *z*-score; WHZ, weight-for-height *z*-score.

a Student's *t*-test, reports $p < 0.01$ in table but $p < 0.001$ in text.

b Differences between groups tested using Cochrane Mantel–Hanzel test.

Quality assessment for primary studies (modified for severe malnutrition)

A. Selection bias

1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	Cannot tell ✓	
2. What percentage of selected individuals participated?	80–100%	60–79%	< 60%	N/A	Cannot tell ✓
Summary of selection bias	*Strong*	*Moderate*	*Weak*		
(Methodological strength of study)			✓		

B. Study design

1. What was the study design?	RCT				
(Please tick appropriate and specify design if categorise as 'Other')	CCT				✓
	Cohort analytic (two group pre + post)				
	Case–control				
	Cohort [one group pre + post (before and after)]				
	Interrupted time series				
	Other – *specify*				
	Cannot Tell				
2. Was the study described as randomised?	Yes	No ✓			

If answer to no. 2 is 'no' complete summary then go to section C. Confounders. If answer is 'yes', answer no. 3 and no. 4 below, before completing summary for this section

3. If answer was yes, was the method of randomisation described?	Yes	No		
4. If answer was yes, was the method appropriate?	Yes	No		
Summary of study design	*Strong*	*Moderate*	*Weak*	
(Methodological strength of study)	✓			

C. Confounders

1. Were there important differences between groups prior to the intervention?	Yes	No ✓	Cannot tell	
2. If yes, indicate the percentage of relevant confounders that were controlled [either in the design (e.g. by stratification or matching) or in the analysis]?	80–100%	60–79%	< 60%	Cannot tell
Summary of confounders	*Strong*	*Moderate*	*Weak*	
(Methodological strength of study)	✓			

D. Blinding

1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Cannot tell ✓	
2. Were the study participants aware of the research question?	Yes	No ✓	Cannot tell	
Summary of blinding	*Strong*	*Moderate*	*Weak*	
(Methodological strength of study)		✓		

E. Data collection methods				
1. Were data collection tools shown to be valid?	Yes ✓	No	Cannot tell	
2. Were data collection tools shown to be reliable?	Yes ✓	No	Cannot tell	
Summary of data collection *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*	
F. Withdrawals and dropouts				
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No ✓	Cannot tell	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100% ✓	60–79%	< 60%	Cannot tell
Summary of withdrawals and dropouts *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*	
G. Intervention integrity				
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100% ✓	60–79%	< 60%	Cannot tell
2. Was the consistency of the intervention measured?	Yes ✓	No	Cannot tell	
3. Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?	Yes	No ✓	Cannot tell	
H. Analysis				
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
3. Are the statistical methods appropriate for the study design?	Yes ✓	No	Cannot tell		
4. Is the analysis performed by intervention allocation status (i.e. ITT) rather than actual intervention received?	Yes ✓	No	Cannot tell		
Global rating for study[a] (Overall methodological strength of study – based on sections A–F)	Strong	Moderate ✓	Weak		

N/A, not applicable.
a Strong = four strong ratings with no weak ratings; moderate = one weak rating; weak = two or more weak ratings.

Simmer *et al.* 1988[77]

Data extraction table

Reference and design

Author: Simmer *et al.*[77]

Year: 1988

Country: Bangladesh

Study design: CCT

Setting: inpatient (Children's Nutrition Unit)

Number of centres: one

Funding: Save the Children Fund (UK); Heinz Fellowship of the British Paediatric Association

Intervention

Intervention: zinc supplement [50 mg of zinc as zinc sulphate ($zincSO_4$) daily or 10 mg/kg daily if weight < 5 kg] for 2 weeks

Control: standard care (no zinc supplement)

Third group: well-nourished children (no details extracted here)

Children were allocated to the two groups after ≥ 3 days and usually after 7 days

Other interventions used: participants were fed milk every 2 hours (80–120 ml/kg/day increasing to 250 ml/kg/day). Weaning food was also given, consisting of rice, dal (pulses) and vegetables. Meat and bananas were often included, oil was added when more calories were required and an egg was added when serum proteins were low. A full diet (three cooked meals and four milk feeds a day) was usually tolerated by the third day. Additional vitamin A (100,000–200,000 IU/day) and ferrous sulphate (4–6 mg/kg/day) were routinely given

A play area with volunteer therapists provided some psychological stimulation for the children

Associated diseases and complications of nutritional rehabilitation, such as hypothermia, hypoglycaemia, and fluid overload, were treated promptly

TB: diagnosed and treated if at least two of the following criteria were met: history of contact, gradual wasting, fever and cough for 1 month, failure to gain weight despite adequate caloric intake, painless enlargement of cervical nodes or pneumonia that failed to respond to antibiotics

Participants

Definition of SAM: not specifically defined; the nutritional diagnosis was based on McLaren's criteria.[105] The Children's Nutrition Unit is specifically for children with third-degree malnutrition, defined as nutritional oedema or W/A < 60% and W/H < 70% of local standards (or < 42% and 63%, respectively, of Western standards)

Number of participants: $N = 25$ (zinc group, $n = 13$; control group, $n = 12$)

Sample attrition/dropout: one patient was excluded from each group

Sample crossovers: none reported

Inclusion criteria:

- 1–7 year-old children
- absence of dehydration
- loss of oedema
- packed cell volume > 0.25
- children who had been at Children's Nutrition Unit for ≥ 3 days and were expected to stay for ≥ 3 weeks

Exclusion criteria: not stated

General characteristics of participants:

- SAM children, average age ≈ 39 months
- tuberculosis: 52%
- pneumonia: 48%
- clinical signs of vitamin A deficiency: 83%

Outcome measures

Primary outcomes: not specifically stated, but appears to be levels of zinc (plasma + polymorphonuclear) and plasma protein

Secondary outcomes: not stated, but appears to be vitamins A and E, ferritin, weight gain, calorie intake and protein intake

Method of assessing outcomes: weight and height measured on admission

Blood was collected at the beginning and, when possible, at the end of the study period for measurement of polymorphonuclear zinc and plasma levels of zinc, vitamins A and E, and ferritin

Zinc concentration was measured by flame atomic absorption spectrophotometry. Vitamin A and vitamin E were measured by high-performance liquid chromatography and ferritin levels by an ^{125}I immunoradiometric assay

(Details on blood collection and preparation for analysis are given by the authors, but have not been extracted)

Protein and calorie intake were calculated daily by the dietitians at Children's Nutrition Unit; the quantity and type of food was recorded and duplicate food samples were collected from seven children aged 24–48 months and ashed for zinc concentration measurement by atomic absorption spectrophotometry

Discharge: usually within 3 weeks if 75–80% W/H (Western standards), haemoglobin > 100 g/l and total serum proteins > 65 g/l. Children with TB were admitted for 6 weeks to ensure adequate drug therapy

Adverse symptoms: medical and nursing staff were aware of the possibility of side effects in the children receiving zinc supplements. Protein and calorie intake of both groups were monitored to study anorexia as a potential adverse effect of zinc supplementation

Length of follow-up: 2 weeks for outcomes although hospital stay was usually 3 weeks (6 weeks for children with TB)

Recruitment dates: NR

Characteristics of participants

Characteristic	Zinc supplemented ($n=12$)	Control (non-supplemented) ($n=11$)	p-value
Age, months (range)	35.3 ± 5 (12–96)	42.8 ± 7.8 (12–96)	NR
Weight, kg	6.7 ± 0.6	7.9 ± 1.1	NR
W/A, %	46 ± 3	48 ± 3	NR
W/H, %	70 ± 2	66 ± 2	NR
Height, cm	76 ± 3	80 ± 5	NR
H/A, %	80 ± 2	78 ± 4	NR
Nutritional diagnosis (McLaren's criteria), *n*			
Marasmus	1	1	NR
Kwashiorkor	5	3	NR
Marasmic kwashiorkor	6	7	NR

Comments: results are reported as mean ± SE unless otherwise stated

No statistically significant differences between groups were reported

Whole group mean age = 38.9 ± 4.6 months, mean weight = 7.3 ± 0.6 kg, mean W/A = 47.1 ± 2.3%, mean W/H = 68.1 ± 1.8%

Birth order, number of living siblings and family income per month and per capita per day are reported, but have not been extracted

Results

Primary outcomes	Zinc supplemented ($n=12$)	Control (non-supplemented) ($n=11$)	p-value
Polymorphonuclear zinc, mmol/10^{10} polymorphonuclear			
On admission	–	–	NR
On entry to study	1.75 ± 0.11	2.05 ± 0.18	NR
On conclusion of study	2.59 ± 0.25[a]	1.60 ± 0.23	NR
Plasma zinc, µmol/l			
On admission	–	–	NR
On entry to study	10.8 ± 0.8	8.6 ± 0.8	NR
On conclusion of study	14.6 ± 0.9[b]	12.3 ± 0.9[c]	NR
Plasma protein, g/dl			
On admission	5.3 ± 0.3	5.1 ± 0.2	NR
On entry to study	6.6 ± 0.4	6.6 ± 0.3	NR
On conclusion of study	7.6 ± 0.2(8)[d]	7.8 ± 0.1(7)[c]	NR

Comments: packed cell volume, ferritin, vitamin A and vitamin E levels were reported but have not been extracted

Overall, plasma zinc and protein levels were weakly correlated ($r=0.56$, $p<0.01$); in the non-supplemented children the correlation between plasma zinc and protein levels was stronger ($r=0.73$, $p<0.001$)

Anthropometric characteristics and the results on plasma zinc, polymorphonuclear zinc, plasma vitamins A and E levels of a non-malnourished, non-supplemented control group were reported, but have not been extracted

Secondary outcomes	Zinc supplemented ($n=12$)	Control (non-supplemented) ($n=11$)	p-value
Mean weight gain, g/day			
Week one	35	32	NR
Week two	70 ± 20	40 ± 10	NR
Weight gain, g/kg/day			
Week one	4.6 ± 1.9	4.9 ± 3.3	NR/NS
Week two	8.83 ± 1.56	5.09 ± 1.62	NR; 95% CI 0.88 to 8.36
Calorie intake, kcal/kg/day			
Week one	161 ± 8	156 ± 8	NR/NS
Week two	180 ± 9	169 ± 9	NR/NS

Protein intake, g/kg/day			
Week one	4.7 ± 0.2	4.6 ± 0.3	NR/NS
Week two	5.3 ± 0.2	4.9 ± 0.3	NR/NS
Per cent who achieved an optimal rate of weight gain (at Children's Nutrition Unit, > 10 g/kg/day)	42	9	< 0.001

Comments: the mean unsupplemented dietary zinc intake of the malnourished children was 3.7 (range 2.4–5.3) mg/d. The zinc contents of individual foods were reported but not extracted

Safety: taking into consideration anorexia as a common feature of severe experimental zinc deficiency in animals, there was no significant difference in the intake of the two groups

Tube feeding was required for a few days for one patient in each group. Two patients in each group had a blood transfusion

HIV: NR

Barriers to implementation

NR

Methodological comments

Participants were randomly selected by the nursing sisters of Children's Nutrition Unit. During nutritional rehabilitation, the mean supplemented dietary in take of zinc was only 3.7 mg/d, which is < 40% the recommended daily allowance. A daily dose of 50 mg probably is unnecessarily large, but did not cause any side effects

Allocation to treatment groups: participants were alternately allocated to groups for a 2-week period

Blinding: no details reported. Would assume no blinding of children, investigators nor outcome assessors

Comparability of treatment groups: reports no differences in baseline characteristics (no *p*-values reported). The incidence of TB, pneumonia and vitamin A deficiency was also similar in both groups

Method of data analysis: all data were expressed as mean ± SE and were analysed by unpaired Student's *t*-test. Not ITT analysis

Sample size/power calculation: NR

Attrition/dropout: one patient was excluded from the zinc group owing to being transferred to the children's hospital with a provisional diagnosis of typhoid fever. One patient was excluded from the control group because two doses (100 mg) of zinc had been accidentally given

General comments

Generalisability: the criteria used to define SAM (McLaren's criteria: < 75% W/H and W/A), differ from the current WHO criteria; however, the average W/H is < 70%. The age inclusion range of 1–7 years differs from SHTAC's protocol (< 5-year-old children), though the mean age was 39 months. It is not clear whether or not these results can be extrapolated to the general population, as the random selection of participants was not detailed by the authors. Many children had comorbidities, such as TB, pneumonia and vitamin A deficiency

Outcome measures: appropriate, though some key outcomes, such as mortality rate, morbidity, and time to recover were NR

Intercentre variability: not applicable

Conflict of interest: NR

IU, international units; NR, not reported; NS, not statistically significant.
a $p < 0.001$, on entry to study vs on conclusion of study.
b $p < 0.01$, on entry to study vs on conclusion of study.
c $p < 0.005$, on entry to study vs on conclusion of study.
d $p < 0.05$, on entry to study vs on conclusion of study.

Quality assessment for primary studies (modified for severe malnutrition)

A. Selection bias

1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely ✓	Not likely	Cannot tell	
2. What percentage of selected individuals participated?	80–100% ✓	60–79%	< 60%	N/A	Cannot tell
Summary of selection bias *(Methodological strength of study)*	*Strong*	*Moderate* ✓	*Weak*		

B. Study design

1. What was the study design? (Please tick appropriate and specify design if categorise as 'Other')	RCT			
	CCT			✓
	Cohort analytic (two group pre + post)			
	Case–control			
	Cohort [one group pre + post (before and after)]			
	Interrupted time series			
	Other – *specify*			
	Cannot Tell			
2. Was the study described as randomised?	Yes	No ✓		

If answer to no. 2 is 'no' complete summary then go to section C. Confounders. If answer is 'yes', answer no. 3 and no. 4 below, before completing summary for this section

3. If answer was yes, was the method of randomisation described?	Yes	No		
4. If answer was yes, was the method appropriate?	Yes	No		
Summary of study design *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*	

C. Confounders

1. Were there important differences between groups prior to the intervention?	Yes	No ✓	Cannot tell	
2. If yes, indicate the percentage of relevant confounders that were controlled [either in the design (e.g. by stratification or matching) or in the analysis]?	80–100%	60–79%	< 60%	Cannot tell
Summary of confounders *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*	

D. Blinding

1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Cannot tell ✓	
2. Were the study participants aware of the research question?	Yes	No	Cannot tell ✓	
Summary of blinding *(Methodological strength of study)*	*Strong*	*Moderate*	*Weak* ✓	

E. Data collection methods				
1. Were data collection tools shown to be valid?	Yes ✓	No	Cannot tell ✓	a
2. Were data collection tools shown to be reliable?	Yes ✓	No	Cannot tell ✓	a
Summary of data collection *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak* ✓	b
F. Withdrawals and dropouts				
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes ✓	No	Cannot tell	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100% ✓	60–79%	< 60%	Cannot tell
Summary of withdrawals and dropouts *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*	
G. Intervention integrity				
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100% ✓	60–79%	< 60%	Cannot tell
2. Was the consistency of the intervention measured?	Yes ✓	No	Cannot tell	
3. Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?	Yes	No ✓	Cannot tell	
H. Analysis				
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
3. Are the statistical methods appropriate for the study design?	Yes ✓	No	Cannot tell		
4. Is the analysis performed by intervention allocation status (i.e. ITT) rather than actual intervention received?	Yes	No ✓	Cannot tell		
Global rating for study[c] (Overall methodological strength of study – based on sections A–F)	Strong	Moderate ✓ (zinc status)	Weak ✓ (weight)		

N/A, not applicable.
a 'Yes' for zinc status, 'cannot tell' for weight.
b 'Strong' for zinc status, 'weak' for weight.
c Strong = four strong ratings with no weak ratings; moderate = one weak rating; weak = two or more weak ratings.

Vasudevan *et al*. 1997[78]

Data extraction table

Reference and design	Intervention	Participants	Outcome measures
Author: Vasudevan *et al.*[78] *Year:* 1997 *Country:* India *Study design:* double-blind placebo-controlled trial *Setting:* outpatient (Division of Department of Paediatric Medical College) *Number of centres:* one *Funding:* not stated	*Intervention:* zinc-supplemented group received 6.6 mg of elemental zinc, equivalent to 20 mg of zinc sulphate, once daily *Control:* placebo was provided in similar looking capsules to zinc supplement *Other comparator group:* normal, healthy children, not malnourished or ill, who were siblings or volunteers were analysed for serum zinc to determine the normal range (outcomes NR) *Other interventions used:* nutritional counselling to parents, dietary intake adjusted to 100–120 calories/kg/day by instructing the mother	*Definition of SAM:* protein energy malnutrition grades III and IV using IAP criteria *Number of participants:* 72 children recruited, 62 children completed designated follow-up period (31 per group) *Sample attrition/dropout:* 10 children (five per group) *Sample crossovers:* not stated *Inclusion criteria*: aged 8–24 months, suffering from protein–energy malnutrition grades III and IV *Exclusion criteria:* children with other concurrent causes of malnutrition by history, physical examination and investigations *General characteristics of participants:* none stated other than inclusion criteria	*Outcomes:* weight of the child; serum zinc. Primary and secondary outcomes were not defined *Method of assessing outcomes:* serum zinc analysis by calorimetric methods using a kit obtained from Randox Laboratories (UK). Weight of the child and serum zinc was assessed at baseline and at 3-months follow-up. Serum zinc was assessed at end of 3 months, allowing 6 days after the last dose of zinc prior to analysis *Adverse symptoms:* none stated *Length of follow-up:* 3 months *Recruitment dates:* none reported

Characteristics of participants

Characteristic	Zinc supplemented ($n=31$)	Placebo ($n=31$)	*p*-value
Mean serum zinc levels	98.4 ± 26.1 µg/dl		

Comments: mean serum zinc levels for healthy group 154.4 ± 24 µg/dl significantly different to malnourished children 98.4 ± 26.1 µg/dl ($p<0.001$)

Results

Outcomes	Zinc supplemented ($n=31$)	Placebo ($n=31$)	*p*-value
Change in zinc levels (µg/dl) (before-and-after study)	+51.3	+16.4	<0.001
Rate of weight gain (g/kg/day)	1.4	0.98	>0.1

Comments: states that none of the children with zinc supplementation developed any related side effects

Safety: none stated

HIV: none stated

Barriers to implementation

None stated

Methodological comments

Allocation to treatment groups: not stated

Blinding: double blind

Comparability of treatment groups: matched for age (within 3 months), sex, W/A, socioeconomic status, ethnic background (data NR)

Method of data analysis: t-tests (paired and Student's)

Sample size/power calculation: not stated

Attrition/dropout: 10 children (five per group) did not complete the designated follow-up. Reasons for dropout were NR

General comments

Generalisability: limited details are provided about the group and so it is only possible to indicate that the study is relevant to children aged 8–24 months with PEM

Outcome measures: suitable outcomes were reported

Intercentre variability: not relevant

Conflict of interest: none stated

NR, not reported.

Quality assessment for primary studies (modified for severe malnutrition)

A. Selection bias

1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely ✓	Not likely	Cannot tell	
2. What percentage of selected individuals participated?	80–100% ✓	60–79%	< 60%	N/A	Cannot tell
Summary of selection bias *(Methodological strength of study)*	*Strong*	*Moderate* ✓	*Weak*		

B. Study design

1. What was the study design? (Please tick appropriate and specify design if categorise as 'Other')	RCT				
	CCT				✓
	Cohort analytic (two group pre + post)				
	Case–control				
	Cohort [one group pre + post (before and after)]				
	Interrupted time series				
	Other – *specify*				
	Cannot Tell				
2. Was the study described as randomised?	Yes	No ✓			

If answer to no. 2 is 'no' complete summary then go to section C. Confounders. If answer is 'yes', answer no. 3 and no. 4 below, before completing summary for this section

3. If answer was yes, was the method of randomisation described?	Yes	No		
4. If answer was yes, was the method appropriate?	Yes	No		
Summary of study design *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*	

C. Confounders

1. Were there important differences between groups prior to the intervention?	Yes	No	Cannot tell ✓	
2. If yes, indicate the percentage of relevant confounders that were controlled [either in the design (e.g. by stratification or matching) or in the analysis]?	80–100%	60–79%	< 60%	Cannot tell
Summary of confounders *(Methodological strength of study)*	*Strong*	*Moderate*	*Weak* ✓	

D. Blinding

1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No ✓	Cannot tell	
2. Were the study participants aware of the research question?	Yes	No ✓	Cannot tell	
Summary of blinding *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*	

E. Data collection methods				
1. Were data collection tools shown to be valid?	Yes ✓ – zinc	No ✓ – weight	Cannot tell	
2. Were data collection tools shown to be reliable?	Yes	No	Cannot tell ✓	
Summary of data collection *(Methodological strength of study)*	*Strong*	*Moderate* ✓ – zinc	*Weak* ✓ – weight	
F. Withdrawals and dropouts				
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No ✓	Cannot tell	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100% ✓	60–79%	< 60%	Cannot tell
Summary of withdrawals and dropouts *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*	
G. Intervention integrity				
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100% ✓	60–79%	< 60%	Cannot tell
2. Was the consistency of the intervention measured?	Yes ✓	No	Cannot tell	
3. Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?	Yes	No ✓	Cannot tell	
H. Analysis				
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
3. Are the statistical methods appropriate for the study design?	Yes ✓	No	Cannot tell		
4. Is the analysis performed by intervention allocation status (i.e. ITT) rather than actual intervention received?	Yes	No ✓	Cannot tell		
Global rating for study[a] (Overall methodological strength of study – based on sections A–F)	Strong	Moderate ✓ – zinc	Weak ✓ – weight		

N/A, not applicable.

a Strong = four strong ratings with no weak ratings; moderate = one weak rating; weak = two or more weak ratings.

Bhutta *et al.* 1999[79]

Data extraction table

Reference and design

Author: Bhutta *et al.*[79]

Year: 1999

Country: Pakistan

Study design: double-blind RCT

Setting: Nutrition Research ward at the National Institute of Child Health

Number of centres: one

Funding: the Applied Diarrhoeal Disease Research Program of the Harvard Institute for International Development via an agreement with the US Agency for International Development

Intervention

Intervention: zinc supplementation (3 mg/kg/day of elemental zinc sulphate, single daily dose) during 14 days of inpatient dietary therapy and continued for 14 days at home (with home available diets) after discharge

Control: placebo during 14 days of inpatient dietary therapy and continued for 14 days at home (with home available diets) after discharge

Other interventions used: applied to all children: stabilisation period of 24 hours during which i.v. and oral rehydration fluids were administered as necessary and antibiotic therapy for concomitant non-enteric infections was initiated. Stool output quantified and and any coexisting dehydration or electrolyte imbalance corrected

Dietary therapy with rice-lentil KY diet, supplemented with vitamins initiated and continued under supervision for 14 days. Diet administered ad libitum, in gradually increasing amounts, to provide at least 100 kcal/kg/day by day 4 of therapy

Details of the diet below

Breastfeeding continued as required

Degree of dehydration, body temperature, vital signs and clinical status recorded twice daily or more frequently as clinically indicated. In cases of suspected septicaemia a blood culture was obtained before initiation of broad-spectrum antibiotics (usually i.v. ampicillin and gentamicin, or i.v. ceftriaxone in suspected typhoidal salmonellosis). Suspected bacterial lower respiratory infections evaluated by chest radiography and treated according to the standard WHO guidelines

Participants

Definition of SAM: not defined, although children were shown to meet W/A and MUAC criteria

Number of participants: $N = 87$ (intervention, $n = 43$; control, $n = 44$)

Sample attrition/dropout: 10 participants did not complete the inpatient part of the study and did not take supplements at home. Zinc group: two discharged prematurely, two because of concomitant infection precluding full enteral feeds, and one because of development of recurrent dehydration. Control: two discharged prematurely, three because of concomitant infection precluding full enteral feeds

Sample crossovers: not applicable

Inclusion criteria: children aged 6–36 months with persistent diarrhoea (four or more unformed stools per day continuously for at least 14 days) and malnutrition (WAZ ≤ 2)

Exclusion criteria:

- children with overt evidence of kwashiorkor and ocular or skin lesions suggestive of vitamin A or zinc deficiency
- children who still needed i.v. fluids or were unable to tolerate oral feeds because of concomitant illness at the end of the 24-hour stabilisation phase were also excluded

General characteristics of participants: children aged 6–36 months with persistent diarrhoea and evidence of malnutrition

Outcome measures

Primary outcome: overall weight gain by day 14 of inpatient therapy

Secondary outcomes (> 14 days inpatient therapy):

- overall energy intake (kcal/kg/day)
- stool frequency (number/day)
- stool volume (g/kg/day) for males
- changes in laboratory parameters (included serum albumin, prealbumin, alkaline phasphatase, insulin-like growth factor-1, plasma copper and zinc)
- time to weight gain
- time to diarrhoeal recovery
- time taken to achieve a 30% and 50% reduction in stool output

Method of assessing outcomes: unclothed weight obtained prior to feed at admission, and daily, on a double-beam balance sensitive up to 10 g. Length measured on an infant stadiometer, occipito-frontal, mid-arm, and mid-thigh circumferences measured using paper tape. Anthropomorphic measures repeated at days 7, 14 and 28

Laboratory measurements were undertaken at baseline, 7 and 14 days

Daily amounts of food consumed estimated by weighing left-over food. Breastfed amount estimated by immediate test weighing

Accurate records of stool, vomitus and urinary output were maintained by quantifying stool output separately from urine by means of adhesive bags. For females, only stool frequency and character were recorded after 72 hours of therapy (because of high rates of urine–stool admixture)

A range of laboratory investigations were carried out at baseline, day 7 and day 14 on stools and blood (details not data extracted).Intestinal permeability was also assessed. Children were considered zinc deficient based on plasma zinc levels < 60 µg/dl (9.18 µmol/l)

Time to weight gain: time taken to achieve weight gain for three or more days consecutively after achieving a caloric intake of 100 kcal/kg/day

Time to diarrhoeal recovery: time taken to achieve a reduction in stool volume to < 30 g/kg/day in males, stool frequency less than four per day in both, and achievement of a semisoft stool consistency

Compliance with therapy: assessed by estimation of remaining supplement volume at return appointment

Adverse symptoms: NR

Length of follow-up: 28 days

Recruitment dates: July 1993 to September 1995

Characteristics of participants

Characteristic	Intervention (zinc) (*n* = 43)	Control (placebo) (*n* = 44)	*p*-value
Sex (M : F)	27 : 16	26 : 18	NS
Age, months	11.6 ± 5.6	13.1 ± 6.2	NS
WAZ	–3.47 ± 0.97	–3.27 ± 1.33	NS
HAZ	–1.68 ± 1.14	–1.44 ± 1.34	NS
WHZ	–3.02 ± 0.90	–3.13 ± 1.19	NS
Mid-arm circumference, cm	11.1 ± 1.5	11.6 ± 1.9	NS
Total protein, g/l	55.0 ± 9.2	56.8 ± 8.9	NS
Serum albumin, g/l	33.7 ± 7.8	33.5 ± 6.5	NS
Serum prealbumin, mg/l	93.8 ± 40.2	77.4 ± 35.0	NS
Haemoglobin, g/l	92.3 ± 18.2	91.6 ± 19.0	NS
Haematocrit, %	29.9 ± 4.3	29.8 ± 4.9	NS
C-reactive protein, mg/l	32.9 ± 42.5	41.4 ± 67.6	NS
Plasma zinc, µg/dl	78.0 ± 32.2	70.3 ± 19.0	NS
Plasma copper, µg/dl	67.4 ± 34.2	64.1 ± 19.2	NS
Duration of diarrhoea 14–30 days	33 (77%)	32 (73%)	NS
> 30 days	10 (23%)	12 (27%)	
Stool at admission, *n* (%)			
Watery	32 (74)	28 (64)	NS
Bloody	3 (7)	2 (5)	
Mucoid	3 (7)	6 (14)	
Mixed	5 (12)	8 (18)	

Stool volume *n* (%)[a]			
< 40 g/kg/day	13 (30)	9 (20)	NS
40–70 g/kg/day	10 (23)	17 (39)	
> 70 g/kg/day	20 (47)	18 (41)	
Stool frequency *n* (%)[a]			
1–5 per day	10 (23)	8 (18)	NS
6–10 per day	14 (33)	15 (34)	
> 10 per day	19 (44)	21 (48)	
Degree of dehydration at admission *n* (%)			
None	23 (53)	29 (66)	NS
Mild	16 (37)	11 (25)	
Moderate	2 (5)	2 (5)	
Severe	2 (5)	2 (5)	

Comments: at baseline, overall, 25 children (29%) had plasma zinc levels < 60 µg/dl (9.18 µmol/l) and were therefore considered zinc deficient. Stool pathogens: enteropathogenic *E. coli* and *Campylobacter jejuni* in two each, *S. paratyphi* and *Aeromonas hydrophilia* in two children in the zinc group, and *V. cholerae* ogawa in one child in the placebo group. Degree of dehydration at admission similar in both groups, amounts of i.v. fluids (not data extracted) and ORS (not data extracted) consumed during initial stabilisation were comparable

Results

Primary outcomes	**Intervention (zinc)**	**Control (placebo)**	***p*-value**
Overall weight increment, g/kg/day	10.3 ± 5.7	8.7 ± 6.5	NS
Weight, kg			
Day 1	6.08 ± 1.32	6.33 ± 1.56	
Day 7	6.27 ± 1.29	6.84 ± 1.41	
Day 14	6.67 ± 1.43	7.13 ± 1.42	0.27[b]

Comments: text indicates that rate of weight gain was slow in children with evidence of systemic infection requiring antibiotics, but numerical data are not presented. These patients were distributed equally between the two groups

Secondary outcomes	**Intervention (zinc), mean ± SD (*n* = 43)**	**Control (placebo), mean ± SD (*n* = 44)**	***p*-value**
Plasma zinc, µg/dl[c]			
Day 1	78.0 ± 32.2	70.3 ± 19.0	
Day 7	100 ± 48	64 ± 20	
Day 14	112 ± 64	68 ± 20	0.03[d]
Caloric intake, kcal/kg/day			
Day 1	83.1 ± 37.5	80.2 ± 28.6	
Day 7	129.6 ± 39.6	123.8 ± 36.9	
Day 14	130.7 ± 46.6	121.1 ± 49.7	0.79[b]
Overall increment in caloric intake, kcal/kg/day	39.9 ± 46.5	40.0 ± 51.3	NS
Stool frequency, *n*/day			
Day 1	10.2 ± 6.4	11.8 ± 7.8	
Day 7	5.9 ± 5.6	5.2 ± 3.7	
Day 14	2.9 ± 1.6	3.0 ± 2.2	0.52[b]
Decrease in stool frequency, *n*/day	7.4 ± 7.4	8.1 ± 8.8	NS

Stool volume, g/kg/day (males)			
Day 1	116.8 ± 103.7	141.9 ± 171.6	
Day 7	66.7 ± 68.1	43.9 ± 40.1	
Day 14	24.9 ± 16.2	27.8 ± 31.4	0.42[b]
Decrease in stool volume (g/kg/day)	91.1 ± 103.6	98.0 ± 187.9	NS
Mid-arm circumference (cm)			
Day 1	11.4 ± 1.5	11.5 ± 1.9	
Day 7	11.7 ± 1.4	12.0 ± 1.8	
Day 14	12.0 ± 1.4	12.4 ± 1.8	0.66[b]
Overall increment in mid-arm circumference	0.3 ± 0.3	0.4 ± 0.3	NS
Weight gain during the 14 days of ambulatory home based supplementation, g/kg/day	9.2 ± 46	7.6 ± 5.7	NS
Increment in mid-arm circumference after 14 days of ambulatory home based supplementation	0.13 ± 0.28	0.19 ± 0.40	NR

Comments: data from Kaplan–Meier plots of time-to-diarrhoeal-recovery and time-to-weight-gain have not been data extracted. Although children in the zinc group had a faster initial reduction in stool output (log-rank test for time to 30% reduction in stool output; $p < 0.03$) there was no significant difference between the groups for the time take for a 50% reduction in stool output ($p = 0.24$). The overall time taken for diarrhoeal recovery ($p = 0.713$) and weight gain ($p = 0.397$) were comparable

The authors performed subgroup analyses on outcomes for the subgroup with low plasma zinc levels at admission (not data extracted), and for the subgroup of stunted children (HAZ < -2) (data not presented in paper). There were no significant differences, but the authors acknowledge that their study had insufficient power to detect significant differences in these subgroups

Data on the lactulose: rhamnose ratio, and the sequential breath hydrogen excretion values were not extracted

Safety: no child had a relapse of diarrhoea and the morbidity patterns were comparable during the 14-day period of home supplementation and follow-up

The authors point out that care is needed when supplementing with single nutrients as some may interfere with the absorption of others. In particular, significant interaction of zinc absorption with copper and iron has been described. Data on plasma copper have not been data extracted from a line figure. A significant trend in reduction of serum copper was seen in the zinc group, whereas values significantly increased in the placebo group by the end of the second week of therapy. Numerical values (as well as the line graph) are provided in the paper, but it is not clear what these correspond to as they do not appear to match expected values on the graph for plasma copper at day 14

HIV: NR

Barriers to implementation

NR

Methodological comments

Zinc dose: the authors note that zinc could have been provided at a fixed daily dose for ease of administration. However, they gave 3 mg/kg/day of elemental zinc in an attempt to evaluate a level of zinc intake that provided almost twice the recommended daily allowance. In addition, this level could also have been emulated from dietary sources subsequently. The dose was also believed to be sufficient for replenishment of plasma zinc levels

Allocation to treatment groups: block randomisation. The randomisation code, maintained by the Pharmacy Department at the Aga Khan University Hospital was not available to the investigators until the end of the study. The pharmacy department were unaware of the identity of enrolled patients

Blinding: described as double blind

Comparability of treatment groups: described as closely comparable for all admission clinical, nutritional, and laboratory parameters. Also comparable for the duration and severity of diarrhoea, as assessed by history as well as during the period of stabilisation. An equal number of children in both groups revealed stool pathogens on cultures

Method of data analysis: A mid-term analysis of morbidity and mortality among the participants was conducted independently by consultants from Applied Diarrhoeal Disease Research Program, and the study was allowed to proceed to conclusion. Final analysis was on an ITT basis, irrespective of length of stay in the study. Differences between groups evaluated for categorical data by chi-squared analysis or Fisher's exact test as appropriate. Differences for continuous data compared by two-tailed Student's *t*-test. Sequential data for primary and secondary outcomes at baseline, day 7 and 14 evaluated by analysis of variance for repeated measures, evaluating the interaction of time trend and treatment effect. Time to event data for the two groups compared by survival analysis using the log-rank test. A subgroup analysis was conducted for the subgroup of children considered zinc deficient. Significance was set at 5%

Sample size/power calculation: reported and reference provided for the formula used. The formula used was for analysis of longitudinal continuous data, and the calculation was based on the known pattern and rate of weight gain (5 ± 3 g/kg/day) in comparably malnourished children with persistent diarrhoea receiving the same KY-based diet. It was estimated that to achieve at least a 30% difference in weight gain after 14 days of therapy, with 80% power and a type 1 error of 0.05, 40 participants would be needed in each group. However, the authors note that although overall weight gain exceeded their initial estimates, the SDs were wide, which led to the possibility that the study had insufficient power to elucidate smaller put potentially significant differences in stool output or weight gain. The authors estimated the final power of the study to detect a 25% difference in rates of weight gain was < 60%

Attrition/dropout: numbers overall and by trial group were provided with reasons

General comments

Generalisability: a doctor and nurse in constant attendance on the ward, this level of supervision might not be possible in all settings. As children with kwashiorkor or symptoms suggestive of vitamin A or zinc deficiency were excluded from this study, the results may not be applicable to these groups

Outcome measures: a primary outcome measure was stated although this outcome was subsequently presented among other results. Outcomes were listed and defined where necessary. Outcome data were presented as mean ± SD

Intercentre variability: not applicable

Conflict of interest: not stated

Dietary therapy

Khitchri (60 g rice, 30 g lentils, 10 g dry weight cottonseed oil and 1 g salt) prepared on site daily. Fresh live yoghurt obtained from a single source. Zinc content estimated to be < 2.5 mg zinc per 100 g. Vitamin mixture (1.5 the daily recommended doses): vitamin A (4500 units, 1.35 mg), vitamin D (600 units, 15 µg), vitamin B1 (2.2 mg), vitamin B2 (1.8 mg), vitamin B6 (1.5 mg), vitamin B12 (4.5 µg), nicotinamide (15 mg), vitamin C (75 mg)

ANOVA, analysis of variance; HAZ, weight-for-age z-score; NR, not reported; NS, not statistically significant; WAZ, weight-for-age z-score; WHZ, weight-for-height *z*-score.

a Observed during initial period of stabilisation.

b *p*-values are for the repeated measures ANOVA which evaluated the interaction of time trend and therapy effect for both groups during 14 days of therapy. All differences are non-significant.

c Estimated by reviewer from line figure.

d Zinc-supplemented children showed a sustained increment in plasma zinc and had significantly higher values at days 7 and 14 in comparison with controls ($p = 0.03$ for time trend, $p = 0.03$ for therapy effect). By day 7 of zinc supplementation only three (8%) of the zinc group had plasma zinc levels < 60 µg/dl.

Quality assessment for primary studies (modified for severe malnutrition)

A. Selection bias

1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely ✓	Somewhat likely	Not likely	Cannot tell	
2. What percentage of selected individuals participated?	80–100% ✓	60–79%	<60%	N/A	Cannot tell
Summary of selection bias *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*		

B. Study design

1. What was the study design? (Please tick appropriate and specify design if categorise as 'Other')	RCT			✓
	CCT			
	Cohort analytic (two group pre + post)			
	Case–control			
	Cohort [one group pre + post (before and after)]			
	Interrupted time series			
	Other – *specify*			
	Cannot Tell			
2. Was the study described as randomised?	Yes ✓	No		

If answer to no. 2 is 'no' complete summary then go to section C. Confounders. If answer is 'yes', answer no. 3 and no. 4 below, before completing summary for this section

3. If answer was yes, was the method of randomisation described?	Yes ✓	No	
4. If answer was yes, was the method appropriate?	Yes ✓	No	
Summary of study design *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*

C. Confounders

1. Were there important differences between groups prior to the intervention?	Yes	No ✓	Cannot tell	
2. If yes, indicate the percentage of relevant confounders that were controlled [either in the design (e.g. by stratification or matching) or in the analysis]?	80–100%	60–79%	<60%	Cannot tell
Summary of confounders *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*	

D. Blinding

1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No ✓	Cannot tell	
2. Were the study participants aware of the research question?	Yes	No ✓	Cannot tell	
Summary of blinding *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*	

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes ✓	No	Cannot tell		
2. Were data collection tools shown to be reliable?	Yes	No	Cannot tell ✓		
Summary of data collection (Methodological strength of study)	*Strong*	*Moderate* ✓	*Weak*		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes ✓	No	Cannot tell		
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100% ✓	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts (Methodological strength of study)	*Strong* ✓	*Moderate*	*Weak*		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100% ✓	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes ✓	No	Cannot tell		
3. Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?	Yes	No ✓	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
3. Are the statistical methods appropriate for the study design?	Yes ✓	No	Cannot tell		
4. Is the analysis performed by intervention allocation status (i.e. ITT) rather than actual intervention received?	Yes ✓	No	Cannot tell		
Global rating for study[a] (Overall methodological strength of study – based on sections A–F)	Strong ✓	Moderate	Weak		

N/A, not applicable.

a Strong = four strong ratings with no weak ratings; moderate = one weak rating; weak = two or more weak ratings.

Manary and Brewster 1997[80]

Data extraction table

Reference and design	Intervention	Participants	Outcome measures
Author: Manary and Brewster[80] *Year:* 1997 *Country:* Malawi *Study design:* double-blind RCT (judged as CCT in quality assessment) *Setting:* inpatient (hospital-based NRU) *Number of centres:* one *Funding:* none reported	*Intervention:* high potassium supplementation (additional 3 mmol/kg potassium above the standard supplement given in corn syrup as a medication, total potassium dose of 7.7 mmol/kg/day in phase one of diet, i.e. first 7 days) *Control:* standard potassium supplementation (3.2 mmol/kg/day of potassium plus placebo of corn syrup given as a medication, total potassium dose of 4.7 mmol/kg/day in phase one of diet, i.e. first 7 days) *Other interventions used:* initial routine medications were cotrimoxazole, albendazole, magnesium (2.8 mmol/kg/day), zinc (40 mg daily as lactate) and multivitamins. Oral rehydration solution and i.v. fluid were used cautiously to avoid excess sodium and fluid loads. Standard regime of mild feeds (see end of table)	*Definition of SAM:* only described as children with kwashiorkor *Number of participants:* $N=116$ (intervention, $n=55$; control, $n=61$) *Sample attrition/dropout:* $n=17$ were excluded because they absconded before completion of the 7-day potassium supplement or placebo (intervention $n=7$, control $n=10$) *Sample crossovers:* none reported *Inclusion criteria:* all children admitted with kwashiorkor to the NRU *Exclusion criteria:* children with oedema owing to renal disease or malarial anaemia *General characteristics of participants:* rural children <3 years of age admitted to hospital with kwashiorkor, with or without diarrhoea or HIV infection, but excluding oedema owing to renal disease or malarial anaemia	*Primary outcomes:* NR *Outcomes:* deaths, clinical sepsis, skin ulcers, per cent weight loss, cough, dyspnoea, duration of hospital stay, irritability, diarrhoea and oedema *Method of assessing outcomes:* daily weight taken plus examination for oedema, fever, respiratory signs, oral ulcers, skin ulcers and irritability Number of days for: cough, duration of hospital stay, irritability, diarrhoea and 2+ or 3+ oedema Number of cases for: dyspnoea Per cent weight loss: assessed by day 7 and by discharge Clinical sepsis: days 2–7 and days 8–24. Diagnosis based on fever, shock without dehydration, dyspnoea or an abrupt change in mental status or general condition (no microbiological investigations to confirm diagnosis) Pedal oedema was graded on a 0–3 scale (1+ = <0.5 cm of pitting oedema of the dorsum of the foot; 3+ = gross oedema of shins and eyelids) Deaths: defined as early if it occurred in the first 5 days; defined as late if it occurred after at least 5 days of NRU treatment; defined as unexpected if there were no clinical indications of a life-threatening complication *Adverse symptoms:* mothers were asked daily for 7 days if child was irritable, anorexic, able to finish the feeds, had diarrhoea, vomiting, a cough or respiratory distress Charts of seriously ill children taken home against medical advice were reviewed blindly if they had received ≥ 7 days of treatment, to decide whether or not they were likely to have died at home and these children were then added to the late deaths *Length of follow-up:* unclear *Recruitment dates:* 10 February 1995 to 16 March 1995

Characteristics of participants

Characteristic		Intervention ($n=48$)	Control ($n=51$)	*p*-value
Mean age, months (SD)		29.3 (14)	27.9 (15)	0.62
Wasting (%)	>–1	9 (19)	8 (17)	NR
W/H (SD)	–2	15 (32)	6 (12)	0.91
z-scores (SD)	–3	12 (26)	20 (42)	NR
Oedema free (SD)	<–3	11 (23)	14 (29)	NR
Mean (SD)		–2.04 (1.20)	–2.40 (1.13)	0.13
Stunting (%)	>–2	11 (23)	5 (10)	NR
H/A (SD)	–3	10 (21)	13 (27)	0.92
(*z*-scores) (SD)	–4	11 (23)	15 (31)	NR
	<–4	15 (32)	15 (31)	NR
Mean (SD)		–3.01 (1.73)	–3.44 (1.25)	0.16
Oedema on admission (%)				
1+		9 (19)	9 (18)	NR
2+		13 (27)	16 (31)	0.90
3+		26 (54)	26 (51)	NR
Rash (%)				
Nil		16 (33)	22 (43)	NR
Mild		16 (33)	15 (29)	0.90
Moderate		13 (27)	9 (18)	NR
Severe		3 (6)	5 (10)	NR
Cough (%)		24 (50)	34 (67)	0.14
Clinical sepsis (%)[a]		4 (8)	7 (14)	0.59
Fever > 38.0 °C (%)		7 (15)	11 (22)	0.52
Haematocrit, mean % (SD)		31 (7)	30 (10)	0.49
Diarrhoea, *n* (%)		16 (33)	19 (37)	0.84
Mean days of diarrhoea before admission (SD)		4.2 (3.1)	4.6 (4.0)	0.56
Severe anorexia (%)		12 (25)	14 (27)	0.96
Irritability (%)		40 (83)	42 (82)	0.89
Skin ulcers (%)		18 (37)	19 (37)	0.86

Comments: clinical signs and symptoms on admission for whole sample: fever (39%), cough (53%), shortness of breath (12%), sore mouth (28%), oral thrush (24%), hair changes (58%), hepatomegaly of > 2 cm below the costal margin (28%) and splenomegaly (10%)

Baseline characteristics only provided for those followed up

Results

Outcomes	Intervention ($n=37$)[b]	Control ($n=41$)[b]	*p*-value
Late death (%)[c]	3 (8)	13 (32)	0.02
Left before discharge (after day 7) (%)	3 (8)	8 (19.5)	0.15
Clinical sepsis (days 2–7) (%)	0 (0)	9 (22)	0.01
Clinical sepsis (days 8–24) (%)	3 (9)	9 (22)	0.05
New skin ulcers, number of cases (%)	4 (11)	13 (33)	0.05
Weight loss by day 7, % (SD)	5.6 (8.0)	4.0 (7.2)	0.36
Weight loss by discharge, % (SD)	4.9 (9.1)	3.8 (10.3)	0.61

Cough, number of days (SD)	2.3 (2.6)	3.9 (2.7)	0.01
Dyspnoea, number of cases (%)	1 (3)	10 (24.4)	0.01
Hospital stay, number of days (SD)	11.6 (0.9)	13.2 (4.9)	0.21
Irritability, number of days (SD)	3.4 (1.7)	3.7 (2.1)	0.47
Diarrhoea, number of days (SD)	0.9 (2.5)	1.5 (1.7)	0.14
Oedema 2+ or 3+, number of days (SD)	2.7 (2.2)	2.7 (2.1)	0.99
Number of deaths in hospital (%)	14 (29.2)[d]	20 (39.2)[d]	0.40
Number of death in			
First 48 hours	6	6	NR
Days 3–5	5	4	NR
Late deaths	3	10	NR
Adjusted late deaths (%)	3/37 (8.1)	13/41 (31.7)	0.02[e]
Causes of late death			
Sepsis	3	3	NR
Anaemia		2	NR
Unexpected		5[f]	NR

Comments: case-fatality rate was reduced by 33% in the intervention group (13/48) compared with the control group (21/51). Note, possible error in *n*/N, as all other information suggests 14/48 and 20/51 deaths

The intervention group had significantly fewer presumed septic episodes (3 vs 18) [OR 8.9 (95% CI 2.2 to 50.9)] respiratory symptoms and new skin ulcerations than controls

Safety: none stated

HIV: no enzyme-linked immunosorbent assays for HIV infection were conducted because of a refusal of consent. Paper reported prevalence figures from unpublished 1993–4 data ($n=519$) as 6% for kwashiorkor patients and 17% for marasmic kwashiorkor patients. Also states that >30% of Blantyre mothers are infected, and the transmission rate (by PCR) at birth is 27%[106] with presumably an additional 14% infected via breast milk;[107] therefore, expected prevalence rates for infants are around 12% before ceasing breastfeeding

Barriers to implementation

Lack of skilled management of individual cases, owing to a variety of constraints which are not readily remediable, were responsible for a case-fatality rate of 34% for kwashiorkor. Authors state that they are attempting the rate through feasible changes in management. Nasogastric tube feeding was used infrequently because of resistance from mothers, reducing the potassium intake in anorexic children

It is suggested that the blanket recommendation of a supplement of 4 mmol/kg is insufficient for phase one and might well be too much for the rapid growth phase when added to the diet. Authors state that although individualising doses of micronutrients as a medication has merits, the constraints at NRU make adding them to the diet a much more convenient option when nursing care is limited

Authors recommend that results can not be extrapolated to this setting, as there are regional differences in the prevalence of potassium depletion in kwashiorkor, which may be related to the mineral content of weaning diets and that additional losses of potassium can occur in stool with diarrhoea (present on admission to the NRU in this study in 33–37% of cases)

Methodological comments

Allocation to treatment groups: described as randomised, but no details provided

Blinding: described as double-blind, placebo-controlled trial. Investigators, health workers and mothers unaware of child's allocation group

Comparability of treatment groups: no significant differences between treatment arms (all *p*-values reported)

Method of data analysis: dichotomous parameters were evaluated as ORs with 95% CI with Fisher's exact test and Yates' corrected *p*-values. Continuous parameters were evaluated using Student's *t*-test (Epi Info version 6)

Sample size/power calculation: none reported

Attrition/dropout: numbers and reasons reported. Discontinuation rates appears to be similar between the two groups

General comments

Generalisability: not generalisable to children with oedema because of renal disease or malarial anaemia who were excluded and also not generalisable to older children. Not all the children may have met the current WHO criteria for SAM, as the sample included children with kwashiorkor categorised as W/H –2

Outcome measures: no primary outcome defined. Outcome measures appear suitable and appropriate

Intercentre variability: not applicable

Conflict of interest: none reported

Diet for all admissions (phase one and phase two)

Phase 1: dried skimmed milk, sugar, vegetable oil and water containing 278 kJ (66 kcal) and 1.0 g of protein per 100 ml. Daily intake per kilogram of body weight was approximately 332 kJ (79 kcal), 1.2 g of protein and 1.5 mmol of potassium. Once oedema, appetite and mental status had improved, children advanced to a phase two diet (generally in the second week of treatment, after completion of the potassium supplement or placebo)

Phase 2: four feeds of high-energy milk 477 kJ (114 kcal) and 4.1 g of protein per 100 ml, as well as two feeds of a local weaning porridge of maize, soya, sugar and oil consisting of 468 kJ (112 kcal) and 3.3 g of protein per 100 ml. Daily intake of 150 mmol/kg/day: 712 kJ (170 kcal), 5.8 g of protein and 7.6 mol of potassium/kg/day. The higher protein intake in phase one was necessitated by the use of a milk-oil-sugar premix for both phases

The protein and energy densities of these diets were similar to those recommended by Waterlow[97] of 336 kJ (80 kcal) and 0.7 g of protein/kg/day in phase one and 735 kJ (175 kcal) and 5.75 g of protein/kg/day in phase two. States that the potassium treatment doses for children in both groups were within the ranges of those recommended for SAM in the scientific literature

NR, not reported; NRU, nutritional rehabilitation unit; PCR, polymerase chain reaction.

a See *Methods of assessing outcomes* for definition.

b Numbers excluded 21 early deaths (intervention, $n=11$; control, $n=10$).

c Includes three controls who left hospital to die at home.

d Thirty-four known deaths in hospital during the study (34% case fatality), of which 21 were early and 13 were late deaths (after day 5). Eleven children (intervention $n=3$, control $n=8$) were taken from hospital before discharge after completing the 7-day trial, but before resolution of oedema and clinical improvement. Figure includes three of these children (all control), which had been assessed blindly to have been seriously ill and unlikely to have survived at home.

e OR 5.3 (95% CI 1.2 to 31.0).

f The children who died unexpectedly had persisting diarrhoea and died between days 9 and 13.

Quality assessment for primary studies (modified for severe malnutrition)

A. Selection bias

1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely ✓	Somewhat likely	Not likely	Cannot tell	
2. What percentage of selected individuals participated?	80–100% ✓	60–79%	< 60%	N/A	Cannot tell
Summary of selection bias	*Strong*	*Moderate*	*Weak*		
(Methodological strength of study)	✓				

B. Study design

1. What was the study design?	RCT			
(Please tick appropriate and specify design if categorise as 'Other')	CCT			✓
	Cohort analytic (two group pre + post)			
	Case–control			
	Cohort [one group pre + post (before and after)]			
	Interrupted time series			
	Other – *specify*			
	Cannot Tell			
2. Was the study described as randomised?	Yes ✓	No		

If answer to no. 2 is 'no' complete summary then go to section C. Confounders. If answer is 'yes', answer no. 3 and no. 4 below, before completing summary for this section

3. If answer was yes, was the method of randomisation described?	Yes	No ✓		
4. If answer was yes, was the method appropriate?	Yes	No		
Summary of study design	*Strong*	*Moderate*	*Weak*	
(Methodological strength of study)	✓			

C. Confounders

1. Were there important differences between groups prior to the intervention?	Yes	No ✓	Cannot tell	
2. If yes, indicate the percentage of relevant confounders that were controlled [either in the design (e.g. by stratification or matching) or in the analysis]?	80–100%	60–79%	< 60%	Cannot tell
Summary of confounders	*Strong*	*Moderate*	*Weak*	
(Methodological strength of study)	✓			

D. Blinding

1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No ✓	Cannot tell	
2. Were the study participants aware of the research question?	Yes	No ✓	Cannot tell	
Summary of blinding	*Strong*	*Moderate*	*Weak*	
(Methodological strength of study)	✓			

E. Data collection methods					
1. Were data collection tools shown to be valid?	Yes	No	Cannot tell ✓		
2. Were data collection tools shown to be reliable?	Yes	No	Cannot tell ✓		
Summary of data collection *(Methodological strength of study)*	*Strong*	*Moderate*	*Weak* ✓		
F. Withdrawals and dropouts					
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes ✓	No	Cannot tell		
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100% ✓	60–79%	< 60%	Cannot tell	
Summary of withdrawals and dropouts *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*		
G. Intervention integrity					
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100% ✓	60–79%	< 60%	Cannot tell	
2. Was the consistency of the intervention measured?	Yes	No ✓	Cannot tell		
3. Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?	Yes	No ✓	Cannot tell		
H. Analysis					
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
3. Are the statistical methods appropriate for the study design?	Yes ✓	No	Cannot tell		
4. Is the analysis performed by intervention allocation status (i.e. ITT) rather than actual intervention received?	Yes	No ✓	Cannot tell		
Global rating for study[a] (Overall methodological strength of study – based on sections A–F)	Strong	Moderate ✓	Weak		

N/A, not applicable.

a Strong = four strong ratings with no weak ratings; moderate = one weak rating; weak = two or more weak ratings.

Philip *et al.* 1982[81]

Data extraction table

Reference and design	Intervention	Participants	Outcome measures
Author: Philip *et al.*[81] *Year:* 1982 *Country:* India *Study design:* CCT *Setting:* inpatient *Number of centres:* one *Funding:* NR	*Intervention:* standard diet + nicotinic acid, 25 mg/kg/day (three divided doses) for 1 month *Control:* standard diet for 1 month Standard diet contained 4 g protein and 200 kcal obtained from K Mix two (supplied by UNICEF), tapioca, sugar, gingelly oil and rice (no further details reported) *Other interventions used:* none reported	*Definition of SAM:* no specific reference made to SAM, only those 'fulfilling the standard criteria for marasmas' (no further details reported) *Number of participants:* $N = 80$ (nicotinic acid, $n = 40$; control, $n = 40$) *Sample attrition/dropout:* none reported *Sample crossovers:* none reported *Inclusion criteria:* standard criteria for marasmus (no reference or details provided) *Exclusion criteria:* none reported. *General characteristics of participants:* marasmic children aged 0–4 years	*Primary outcomes:* weight gain *Secondary outcomes:* calorie consumption *Method of assessing outcomes:* weight was recorded every morning before being given the standard diet. The calculated amount of food was given five times daily at 0700, 1000, 1300, 1600 and 2100 hours in divided quantities for 1 month. No further details *Adverse symptoms:* none reported *Length of follow-up:* none beyond the 1 month treatment period *Recruitment dates:* 1974–6

Characteristics of participants

Characteristic	Nicotinic acid ($n = 40$)	Standard diet ($n = 40$)	*p*-value
Age (years), *n* (%)			
0–1	10 (25)	7 (17.5)	NR
1–2	22 (55)[a]	23 (57.5)	NR
2–3	7 (17.5)	8 (20)	NR
3–4	1 (2.5)	2 (5)	NR

Comments: no difference in sex distribution was noted. No other baseline characteristics were reported by the authors

Results

Primary outcomes	Nicotinic acid ($n = 40$)	Standard diet ($n = 40$)	*p*-value
Weight gain in 1 month, g/kg	231.05 (20.05)	171.81 (22.01)	0.001[b]

Comments: results are reported as mean (SD)

When weight gain was calculated separately for each week, both groups showed maximum gain during week 2, followed by week 3, with the lowest gain in weeks 1 and 4 (no data reported)

For both groups, the rate of weight gain was slightly higher in those children with a greater initial weight deficit

Secondary outcomes	Nicotinic acid ($n = 40$)	Standard diet ($n = 40$)	*p*-value
Calories consumed for 1 g gain in weight	14.2	19.3	NR

Safety: none of the children experienced any remarkable side effects of nicotinic acid

HIV: NR

Barriers to implementation

NR

Methodological comments

Allocation to treatment groups: not randomised. No details on allocation

Blinding: NR. No details on how nicotinic acid administered and thus blinding of patients, care providers and outcome assessors is unknown

Comparability of treatment groups: age is the only baseline characteristic reported; the distribution of the age ranges from 0–4 years was similar between the two groups, but no comment or *p*-value was reported. Authors noted that there was no difference in sex distribution (no data or *p*-value)

Method of data analysis: ITT analysis as data at end of study period is for all 80 subjects. No further details reported

Sample size/power calculation: NR

Attrition/dropout: none reported. Data at 1 month is for all included subjects so assume no dropouts

General comments

Generalisability: unable to tell whether or not the included children would meet the current WHO criteria as no specific definition of SAM was given; majority of children < 2 years. Unable to compare these children to the general SAM population as no baseline characteristics were given and reporting is limited

Outcome measures: primary outcome of weight gain was appropriate although mortality was NR

Intercentre variability: N/A

Conflict of interest: no details on funding nor any conflicts of interest were reported

N/A, not applicable; NR, not reported.
a Reported as 65%, but 22/40 = 55%.
b Reports $t = 13.05$ (assume Student's *t*-test value).

Quality assessment for primary studies (modified for severe malnutrition)

A. Selection bias

1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely	Somewhat likely	Not likely	Cannot tell ✓	
2. What percentage of selected individuals participated?	80–100% ✓	60–79%	< 60%	N/A	Cannot tell
Summary of selection bias *(Methodological strength of study)*	*Strong*	*Moderate*	*Weak* ✓		

B. Study design

1. What was the study design? (Please tick appropriate and specify design if categorise as 'Other')	RCT CCT Cohort analytic (two group pre + post) Case–control Cohort [one group pre + post (before and after)] Interrupted time series Other – *specify* Cannot Tell			✓
2. Was the study described as randomised?	Yes	No ✓		

If answer to no. 2 is 'no' complete summary then go to section C. Confounders. If answer is 'yes', answer no. 3 and no. 4 below, before completing summary for this section

3. If answer was yes, was the method of randomisation described?	Yes	No		
4. If answer was yes, was the method appropriate?	Yes	No		
Summary of study design *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*	

C. Confounders

1. Were there important differences between groups prior to the intervention?	Yes	No	Cannot tell ✓	
2. If yes, indicate the percentage of relevant confounders that were controlled [either in the design (e.g. by stratification or matching) or in the analysis]?	80–100%	60–79%	< 60%	Cannot tell
Summary of confounders *(Methodological strength of study)*	*Strong*	*Moderate*	*Weak* ✓	

D. Blinding

1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Cannot tell ✓	
2. Were the study participants aware of the research question?	Yes	No	Cannot tell ✓	
Summary of blinding *(Methodological strength of study)*	*Strong*	*Moderate*	*Weak* ✓	

E. Data collection methods				
1. Were data collection tools shown to be valid?	Yes	No	Cannot tell ✓	
2. Were data collection tools shown to be reliable?	Yes	No	Cannot tell ✓	
Summary of data collection *(Methodological strength of study)*	*Strong*	*Moderate*	*Weak* ✓	
F. Withdrawals and dropouts				
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes	No ✓	Cannot tell	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100% ✓	60–79%	< 60%	Cannot tell
Summary of withdrawals and dropouts *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*	
G. Intervention integrity				
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100%	60–79%	< 60%	Cannot tell ✓
2. Was the consistency of the intervention measured?	Yes	No	Cannot tell ✓	
3. Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?	Yes	No ✓	Cannot tell	
H. Analysis				
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
3. Are the statistical methods appropriate for the study design?	Yes ✓	No	Cannot tell		
4. Is the analysis performed by intervention allocation status (i.e. ITT) rather than actual intervention received?	Yes ✓	No	Cannot tell		
Global rating for study[a] (Overall methodological strength of study – based on sections A–F)	Strong	Moderate	Weak ✓		

N/A, not applicable.

a Strong = four strong ratings with no weak ratings; moderate = one weak rating; weak = two or more weak ratings.

Vásquez-Garibay 2005[82]

Data extraction table

Reference and design	Intervention	Participants	Outcome measures
Author: Vásquez-Garibay[82] *Year:* 2005 *Country:* Mexico *Study design:* RCT *Setting:* inpatient (Unit of Studies of Infantile Nutrition, Metabolic ward, Unit of Studies of Infantile Nutrition, Civil Hospital of Guadalajara) *Number of centres:* one *Funding:* none reported	*Intervention*: added NT (NT+) (SMA; Wyeth de México, SA de CV, Mexico): a milk-based formula with NT and corn syrup added to increase energy density to 3.35 kJ/ml (casein-dominant formula) (see end of table for details) *Control:* no added NT (NT–) (S26; Wyeth de México, SA de CV, Mexico): similar formula with the same energy density, but no added NT (whey-dominant formula) (see end of table for details) Feeding was through a nasogastric tube with infant formula (3.35 kJ/ml) for 2 weeks and ad libitum for a further 2 weeks *Other interventions used:* parasites found in faeces were treated prior to acceptance into study	*Definition of SAM:* W/A or W/H <–3 SD from the median using the NCHS/WHO reference *Number of participants: N* = 25 (NT+, *n* = 12; NT–, *n* = 13) *Sample attrition/dropout : n* = 5 NT+: *n* = 1 (excluded owing to a non-determined liver disease) NT–: *n* = 4 (excluded owing to fever syndrome *n* = 1, emetic syndrome *n* = 1, poor nutritional progress and a positive HIV test *n* = 2) *Sample crossovers:* none reported *Inclusion criteria:* ■ full-term infants with normal birth weight, primary and severe PEM, aged 3–18 months, W/A or W/H <–3 SD from the median NCHS/WHO standard ■ infants with severe PEM, free of infection and/or moderate or severe episodes of diarrhoea (infants with less than four liquid or semi-liquid stools) were accepted ■ only infants with the same clinical type of severe and primary PEM (marasmus) were investigated *Exclusion criteria:* ■ infants rejecting formula feeding ■ genetic, congenital, chronic and/or severe pathologies (Down's syndrome, mucoviscidosis, congenital cardiac disease, cerebral palsy, kidney disease and others) ■ infant's clinical condition might be detrimental to the completion of the study ■ voluntary discharge ■ non-compliance by parent or legal guardian ■ any other pathology contraindicating oral or enteral feeding *General characteristics of participants:* Infants aged 3–18 months with severe PEM and who are free of infection and moderate or severe diarrhoea	*Primary outcomes:* not specifically reported *Outcomes:* weight, length, head circumference, arm circumference, triceps, subscapular, subcostal and suprailiac skin fold thickness *Method of assessing outcomes:* specialised personnel took care of the infants for the duration of the study. Two observers carried out the measurements Anthropometric measurements were taken at start of study and once a week for 4 weeks. Blood samples were obtained by antecubital venopuncture at the start of study (at 0700 hours prior to first feed), after 2 weeks and at end of study (see end of table for details) Weight: taken in a calibrated scale without clothes (Bame model 440, Mexico; with a minimum of 5 g). Before and after each bottle feed, bottles were weighed on a triple-beam balance (Ohaus, Florhand Park, New Jersey) Length: measured on infant-measuring board (read to the nearest 0.1 cm) Age and measurements of length and weight, W/A, L/A and W/L, were calculated and expressed as *z*-scores. Head circumference, arm circumference, and triceps, subscapular, subcostal and suprailiac skin fold thickness were determined with a Lange Skinfold Caliper (Cambridge Scientific Industries, Inc, Cambridge, Maryland) *Definitions:* ■ primary PEM: cause of malnutrition was an inadequate and insufficient diet commonly associated with repeated upper respiratory tract infectious disease and/or frequent diarrhoea ■ severe PEM: free of infection and/or moderate or severe episodes of diarrhoea (infants with less than four liquid or semi-liquid stools) *Adverse symptoms:* none reported *Length of follow-up:* 4 weeks *Recruitment dates:* March 1996 to February 1999

Characteristics of participants

Characteristic	NT+ ($n=11$)	NT– ($n=9$)	p-value
Mean birth weight, g (SD)	2975 (387)	3021 (369)	0.81
Mean age, days (SD)	228 (138)	242 (173)	0.84
Mean age, months (SD)	7.6 (4.6)	8.1 (3.2)	NR
Sex, M : F	8 : 3	5 : 4	NR
Mean weight, g (SD)	4246 (1403)	3955 (1250)	0.87
Mean length, cm (SD)	61.1 (8.0)	60.2 (7.7)	0.95
Mean head circumference, cm (SD)	39.7 (3.4)	38.9 (2.1)	0.85
Mean arm circumference, cm (SD)	7.9 (1.1)	7.6 (1.0)	0.44
Mean triceps, mm (SD)[a]	3.8 (1.0)	2.8 (0.6)	0.031
Mean subscapular, mm (SD)[a]	2.9 (0.7)	2.4 (0.6)	0.076
Mean subcostal, mm (SD)[a]	2.3 (0.5)	1.8 (0.3)	0.045
Mean suprailiac, mm (SD)[a]	2.2 (0.5)	1.7 (0.3)	0.020
Mean total upper arm area, mm^2 (SD)	512 (139)	463 (114)	0.54
Mean upper arm muscle area, mm^2 (SD)	369 (89)	361 (84)	0.82
Mean upper arm fat area, mm^2 (SD)	143 (53)	101 (33)	0.003
Mean arm fat index, % (SD)	27 (4)	22 (2)	0.005
Mean BMI (SD)	11.0 (0.9)	10.6 (1.0)	0.33
W/H mean z-score (SD)	–2.80 (0.73)	–2.99 ± 0.74	0.001

Results

Outcomes: indicator[b]	NT+ ($n=11$)	NT– ($n=9$)	p-value[c]
Mean skin fold, mm (SD)			
Triceps			
Initial	3.8 (1.0)	2.8 (0.6)	0.031
Fourth week	9.2 (2.6)	8.5 (1.6)	0.517
Subscapular			
Initial	2.9 (0.7)	2.4 (0.6)	0.076
Fourth week	8.1 (2.7)	6.4 (1.1)	0.112
Subcostal			
Initial	2.3 (0.5)	1.8 (0.3)	0.045
Fourth week	5.5 (1.9)	4.0 (0.6)	0.004
Suprailiac			
Initial	2.2 (0.5)	1.7 (0.3)	0.02
Fourth week	5.7 (2.5)	4.2 (0.6)	0.114
Body composition, mean (SD)			
Total upper arm area, mm^2			
Initial	512 (139)	463 (114)	0.54
Fourth week	960 (199)	903 (148)	0.49
Upper arm muscle area, mm^2			
Initial	369 (89)	361 (84)	0.82
Fourth week	571 (73)	508 (112)	0.83
Upper arm fat area, mm^2			
Initial	143 (54)	101 (33)	0.003
Fourth week	443 (154)	395 (84)	0.42
Arm fat index, %			
Initial	27 (4)	22 (2)	0.005
Fourth week	45 (8)	44 (7)	0.76

BMI, kg/m^2			
Initial	11.0 (0.9)	10.6 (1.0)	0.33
Fourth week	15.1 (1.0)	14.5 (1.0)	0.23
Mean weight gain, g/day (SD)	67 (15)	69 (12)	
W/H mean *z*-score (SD), fourth week	–0.64 (0.66)	–0.94 (0.47)	0.001

Comments: both NT+ and NT– showed significant improvement in W/A and W/L indices from the first week; however, *p*-values were reported for within group differences only. Mean weight gain was similar between groups (no *p*-value reported)

Paper talks of W/A and W/L, but only outcomes for W/L and L/A are provided (not W/A)

Typical weight gain was five times higher than that of normal infants aged around 8 months and the pace of linear growth was doubled

Other outcomes	**NT+ (*n*=11)**	**NT– (*n*=9)**	***p*-value**
Mean urea concentration, mg/l (SD)	136 (36)	214 (66)	0.009
Mean alkaline phosphatase, U/l (SD)	152 (77)	218 (46)	0.041

Comments: both groups were integrated for initial vs final outcome comparison of creatinine, glucose, calcium and phosphorus levels, showing significant improvements in each for the whole group. The same was true for haemoglobin levels and mean corpuscular volume. There were no significant changes in white blood cell count

Safety: NR

HIV: although not specifically part of the exclusion criteria, two infants with positive HIV tests were excluded

Barriers to implementation

None reported

Methodological comments

Allocation to treatment groups: random assignment into two groups following an arbitrary schedule precisely. When one patient was eliminated, another one was included, receiving the formula that corresponded to the next number in the random sample

Blinding: none reported

Comparability of treatment groups: baseline age, weight and length were similar, although fat stores were slightly higher in the NT+ group. However, apart from significant differences in skin fold, there were also significant baseline differences in upper-arm muscle area, upper-arm fat area and arm fat index between the groups

Method of data analysis: paired Student's *t*-tests for the analysis of all initial vs weekly anthropometric indicators (including initial vs final means of the biochemical and haematological indicators). Non-paired Student *t*-tests were used to compare the anthropometric, biochemical and haematologic mean indicators of group NT+ vs group NT– at different stages in the study. Dbase-IV (Microsoft Corporation, Redmond, WA, USA), Epi Info 6.04 and SPSS/PC programmes were used for capturing, processing and analysing data. Null hypothesis was rejected with a *p*-value of ≤ 0.05

Sample size/power calculation: sample size calculated at 12 for each group (calculations reported). Authors state that the sample size was large enough to compare both groups, considering they had similar means and SDs in most of the anthropometric indicators at the end of the study. However, after exclusions, number of participants was below the sample size needed

Attrition/dropout: number of exclusions and reasons reported

General comments

Generalisability: only to full-term infants with normal birth weight, with primary and severe PEM aged 3–18 months were included. Generalisability might therefore not extent to older children or to children with below birth weight. Definition of SAM meets the WHO criteria

Outcome measures: outcomes appear appropriate

Intercentre variability: N/A, one centre only

Conflict of interest: none reported

Milk-based infant formulas[d]	**NT+ (SMA)**	**NT– (S26)**
Nutrients (per litre)		
Energy, kJ	2845	2800
Fat, g	36	33.9
Linoleate, g	–	7.99
Protein, g	15	14.9
Carbohydrate, g	72	75.9
Mineral salts (ashes), g	2.5	2.0
Sodium, mg	150	156
Potassium, mg	560	659
Chloride, mg	380	429.5
Calcium, mg	420	419.5
Phosphorus, mg	280	210

Vitamin A, IU	2000	1998
Vitamin D, IU	400	400
Vitamin E, IU	19	17.9
Vitamin K, µg	55	54.9
Vitamin C, mg	55	53.9
Thiamin B1, µg	670	400
Riboflavin B2, µg	1000	899
Niacin, µg	5000	4995
Vitamin B6, µg	420	499.5
Folic acid, µg	50	59.9
Pantothenic acid, µg	2100	2992
Vitamin B12, µg	1.3	1.3
Biotin, µg	15	14.6
Choline, mg	100	49.9
Magnesium, mg	35	40
Iron, mg	12	8
Iodine, µg	60	33
Copper, µg	470	413
Zinc, mg	5	5
Manganese, µg	100	46.9

Commercially available formulas with NT (in milligrams per liter) cytidine monophosphate (16.5), uridine monophosphate (5.0), adenosine monophosphate (4.0), guanosine monophosphate (2.0) and inosine monophosphate (2.0) (SMA; 2845 kJ/L); and without NT (S26; 2800 kJ/L). Both formulas, belonging to the same batch, had a similar nutritional content and were within the accepted range for infant formula. The formula was placed in a feeding bag of 500 ml (Pisa; Guadalajara, Jalisco, Mexico), then introduced into a feeding tube (D-731 o 732; Desvar de Mexico, Sociedad Anónima, Mexico) and administered to infants by continuous infusion pump (Braun, Germany)

From day 1*:* daily oral vitamins (vitamin A 5000 IU, vitamin D 1000 IU, vitamin C 50 mg, thiamin 1 mg, riboflavin 0.8 mg, niacin 6 mg and folic acid 0.5 mg)

During the first 5 days: energy intake = 670 kJ/kg/day, protein intake 3.2 g/kg/day

After day 5: depending on the new weight (kilograms), the energy and protein intake was adjusted to 837 kJ/kg/day and 4 g/kg/day, respectively

From day 6*:* elemental iron 3 mg/kg daily

Start of third week: infants were fed ad libitum by bottle. The total amount of formula, protein and energy intake was calculated daily. The formula included all the water, energy, proteins and other nutrients required. No other foods were offered during the 4-week nutritional period (infants were started with complementary foods before being discharged)

Laboratory tests: blood samples at start for total proteins, serum albumin, calcium, phosphorus, magnesium, alkaline phosphatase, urea, creatinine, glucose, sodium, potassium, chloride and haemoglobin, as well as urine analysis. The calcium, phosphorus, magnesium and total protein determinations were done by the final point colorimetric method (RA-1000 Technicon; Bayer Diagnostic, Tarrytown, NY); alkaline phosphatase, by an enzymatic method of zero order and a C-405 filter; and haemoglobin, by a modified haemiglobincyanide method (CELL-DYN 3500R; Abbott Laboratories, Diagnostics Division, North Chicago, IL, USA)

IU, international units; L/A, length-for-age; N/A, not applicable; NR, not reported.

a Skin fold.

b Denotes $p < 0.001$; initial vs fourth week within each group.

c Denotes that some *p*-values are differences between group. Because of the absence of further notations, it is uncertain which *p*-values are for within group and which for between group differences. However, authors state that there were no significant differences between groups at week 4 for total upper arm area, upper arm muscle area, upper arm fat area or arm fat index.

d Powder infant formula; Wyeth de México, Sociedad Anónima de Cuenta variable.

Quality assessment for primary studies (modified for severe malnutrition)

A. Selection bias

1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely ✓	Somewhat likely	Not likely	Cannot tell	
2. What percentage of selected individuals participated?	80–100% ✓	60–79%	< 60%	N/A	Cannot tell
Summary of selection bias	*Strong*	*Moderate*	*Weak*		
(Methodological strength of study)	✓				

B. Study design

1. What was the study design?	RCT			✓
(Please tick appropriate and specify design if categorise as 'Other')	CCT			
	Cohort analytic (two group pre + post)			
	Case–control			
	Cohort [one group pre + post (before and after)]			
	Interrupted time series			
	Other – *specify*			
	Cannot Tell			
2. Was the study described as randomised?	Yes ✓	No		

If answer to no. 2 is 'no' complete summary then go to section C. Confounders. If answer is 'yes', answer no. 3 and no. 4 below, before completing summary for this section

3. If answer was yes, was the method of randomisation described?	Yes ✓	No		
4. If answer was yes, was the method appropriate?	Yes ✓	No		
Summary of study design	*Strong*	*Moderate*	*Weak*	
(Methodological strength of study)	✓			

C. Confounders

1. Were there important differences between groups prior to the intervention?	Yes ✓	No	Cannot tell	
2. If yes, indicate the percentage of relevant confounders that were controlled [either in the design (e.g. by stratification or matching) or in the analysis]?	80–100%	60–79%	< 60%	Cannot tell ✓
Summary of confounders	*Strong*	*Moderate*	*Weak*	
(Methodological strength of study)			✓	

D. Blinding

1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Cannot tell ✓	
2. Were the study participants aware of the research question?	Yes	No	Cannot tell ✓	
Summary of blinding	*Strong*	*Moderate*	*Weak*	
(Methodological strength of study)			✓	

E. Data collection methods				
1. Were data collection tools shown to be valid?	Yes ✓	No	Cannot tell	
2. Were data collection tools shown to be reliable?	Yes	No	Cannot tell ✓	
Summary of data collection *(Methodological strength of study)*	*Strong*	*Moderate* ✓	*Weak*	
F. Withdrawals and dropouts				
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes ✓	No	Cannot tell	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100% ✓	60–79%	< 60%	Cannot tell
Summary of withdrawals and dropouts *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*	
G. Intervention integrity				
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100% ✓	60–79%	< 60%	Cannot tell
2. Was the consistency of the intervention measured?	Yes ✓	No	Cannot tell	
3. Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?	Yes	No ✓	Cannot tell	
H. Analysis				
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
3. Are the statistical methods appropriate for the study design?	Yes ✓	No	Cannot tell		
4. Is the analysis performed by intervention allocation status (i.e. ITT) rather than actual intervention received?	Yes	No ✓	Cannot tell		
Global rating for study[a] (Overall methodological strength of study – based on sections A–F)	Strong	Moderate	Weak ✓		

N/A, not applicable.

a Strong = four strong ratings with no weak ratings; moderate = one weak rating; weak = two or more weak ratings.