Appendix 9

Question 22: data extraction tables

Alam *et al.* 2000[51]

Data extraction table

Reference and design	Intervention	Participants	Outcome measures
Author: Alam *et al.*[51] *Year:* 2000 *Country:* India *Study design:* double-blind RCT *Setting:* inpatient (diarrhoea training and treatment unit) *Number of centres:* one *Funding:* Department of Pediatrics, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh (material and preparation of ORS)	*Intervention:* H-ORS (see end of table for details) *Control:* standard WHO-ORS 75 ml/kg of ORS to be taken in 4 hours for both groups following study inclusion (five sachets formulated in 1 litre of water) (see end of table for details) *Other interventions used:* if severely dehydrated, 50 ml/kg of i.v. RL in first hour prior to study inclusion A single dose of doxycycline (8 mg/kg) was administered to all with clinical suspicion of cholera or positive stool for motile organisms and dose was repeated if the child vomited within half an hour of taking the drug Indications for i.v. fluids were severe dehydration, persistent vomiting (> 3 hours) and persistent dehydration at the end of 4 hours of oral rehydration therapy. 75 ml/kg of RL were given in the next 3 hours and then the child was put back on the study ORS Khichri, Dalia, curds and banana feeds were offered once hydration improved breastfeeding was continued throughout	*Definition of SAM:* W/H < 70%, assessed as per the NCHS, but W/A (not height) is reported in the results *Total:* $n = 170$ (88 H-ORS, 82 WHO-ORS) *Number of SAM participants:* H-ORS $n = 41/88$ (47%), cholera $n = 19/35$, non-cholera $n = 69/135$; WHO-ORS $n = 40/82$ (49%), cholera $n = 16/35$, non-cholera $n = 66/135$ *Total sample attrition/dropout:* $n = 19/170$ (11%) ; dropouts $n = 11$; removed $n = 8$, treatment failures put on WHO–ORS *Sample crossovers:* none *Inclusion criteria:* children with acute (< 4 days duration) diarrhoea with dehydration and > 3 months of age with clinical suspicion of cholera aged 3 months – 5 years with non-cholera diarrhoea *Exclusion criteria:* children with clinical evidence of systemic infection, encephalopathy, electrolyte imbalance, convulsions or invasive diarrhoea *General characteristics of participants:* children aged from 3 months to 5 years with cholera and acute non-cholera diarrhoea	*Primary outcomes:* not specifically reported *Outcomes:* ■ per cent weight gain ■ caloric intake (kcal/kg/day) ■ rehydration phase – frequency (stools/4 hours), ORS consumed (litres) and duration (hours) ■ maintenance phase – frequency (stools/4 hours), ORS consumed (litres) and duration (hours) ■ overall – frequency (stools/4 hours) ORS consumed (litres) and duration (hours) ■ serum sodium (mEq/l) ■ urine output (boys; ml/kg/hour) ■ intravenous fluids (ml/kg) *Method of assessing outcomes:* timescale for rehydration and maintenance phases not defined Intake output records and assessment of dehydration measured four hourly Nutritional status assessed as per NCHS *Recovery and discharge criteria:* non-cholera diarrhoea – three consecutive semi-formed stools or no stools for 12 hours; cholera – no dehydration for 8 hours or no stools for 6 hours Stool: frequency recorded by mother (tally marking). Motile organisms and stool culture was completed for all. Culture was collected on sterile rectal swab and stored in 'Careyblair's media' and plated within 12 hours

Urine: output collected for boys during initial 24 hours

Weight: taken at admission, end of rehydration and discharge

Serum sodium*:* estimation was done at 24 hours

Adverse symptoms: NR

Length of follow-up: none reported, but appears to be until recovery (see definition above)

Recruitment dates: only states that authors enrolled until August 1998

Comments: H-ORS treatment failures were transferred to WHO-ORS. Treatment failure definition: dehydration > 72 hours, diarrhoea > 7 days, consumption of ORS > 8 litres in < 5 years age group, or > 10 litters in > 5 years age group and needing i.v. fluids > 150 ml/kg. Children leaving study prior to recovery were considered treatment failures, if they had dehydration and or frequency of stools

Characteristics of participants

Characteristic SAM only	H-ORS ($n=41$)	WHO-ORS ($n=40$)	*p*-value
Mean age, month (SD)	25.29 (2.09)	24.17 (2.23)	NR
Mean W/A, % (SD)	52.4 (1.64)	58.6 (1.12)	NR

Comments: total sample only. There were no significant differences in the two groups at admission for mean duration (95% CI 11.9 to 20.5; $p=0.6$) and frequency (95% CI 1.1 to 1.4; $p=0.79$) of diarrhoea, whereas the per cent of children with vomiting (OR 1.06, 95% CI 0.43 to 2.31), with some (OR 0.89, 95% CI 0.71 to 1.12) or severe (OR-1.61, 95% CI 0.59 to 4.33) dehydration and those receiving ORS (OR 0.74, 95% CI 0.24 to 2.22) at admission, were comparable. NR for SAM

CI for children with vomiting was reported as 96%. This is assumed to be an error, as all other CIs were reported as 95%

Results

Outcomes, mean (SD)	H-ORS ($n=41$)	WHO-ORS ($n=40$)	*p*-value (95% CI)
Weight gain (%)	4.54 (1.79)	4.45 (2.18)	Not significantly different (*p*-value NR)
Caloric intake (kcal/kg/day)	42.72 (1.66)	39.73 (2.03)	Not significantly different (*p*-value NR)
Rehydration frequency (stools/4 hours)	4.27 (2.029)	5.86 (1.73)	$p=0.32$[a,b] (0.55 to 0.97)
Rehydration ORS consumed (litres)	1.45 (0.002)	1.55 (0.002)	Not significantly different (*p*-value NR)
Rehydration duration (hours)	10.95 (2.23)	11.72 (2.26)	Not significantly different (*p*-value NR)
Maintenance frequency (stools/4 hours)[c]	1.72 (1.92)	2.45 (2.17)	$p=0.035$[a] (0.51 to 0.97)
Maintenance-ORS consumed (litres)[c]	0.69 (0.005)	0.74 (0.01)	Not significantly different (*p*-value NR)
Maintenance duration (hours)[c]	10.45 (2.09)	16.36 (2.01)	$p=0.007$[a] (0.46 to 0.88)
Overall frequency (stool/4 hours)	3.39 (1.80)	4.70 (1.68)	$p=0.011$[a] (0.56 to 0.93)
Overall ORS consumed (litres)	2.74 (0.0017)	3.32 (0.0017)	Not significantly different (*p*-value NR)
Overall duration (hours)	24.35 (1.57)	30.12 (1.69)	Not significantly different (*p*-value NR)
Serum sodium (mEq/l)	134.89 (1.03)	137.03 (1.03)	Not significantly different (*p*-value NR)
Urine output (boys) (ml/kg/hour)[d]	55.79 (1.65)	55.73 (1.89)	Not significantly different (*p*-value NR)
i.v. fluids (ml/kg)[e]	121.23 (1.81)	70.73 (1.51)	Not significantly different (*p*-value NR)

Other (total sample): treatment failure $n=12/170$ (7%); H-ORS $n=3/88$, WHO-ORS 9/82 (OR 0.28, 95% CI 0.07 to 1.1)

Discharged $n=151$ (two children recovered after rehydration phase)

The paper also reported results for H-ORS vs WHO-ORS in total cases and for H-ORS vs WHO-ORS in non-cholera diarrhoea. These were not data extracted. However, the significant results for the SAM subgroup were in the same direction as the results for H-ORS vs WHO-ORS in total cases

Safety: NR

HIV: not applicable

Barriers to implementation

None reported

Methodological comments

Allocation to treatment groups: cases were serially allotted the study ORS packet

Blinding: states double-blind trial; packets of sachets were reported to be identical. No details reported on blinding of outcome assessors

Comparability of treatment groups: characteristics in whole group were reported to be compatible at admission (*p*-value or OR plus 95% CI given). Only age and W/A reported for SAM group and not significantly different (*p*-value not given)

Method of data analysis: analyses of different parameters were conducted in the re-hydration phase, in the maintenance phase, for overall combined data, for children split into cholera/non-cholera and repeated for children with W/H < 70% (but W/A reported in tables) and breast fed/non-breastfed children < 2 years old using SPSS (Version 7.5; SPSS Inc., Chicago, IL, USA). Variables with skewed distribution were log transformed and two-tailed Student's *t*-test used to compare the groups. Chi-squared tests were used to correlate the qualitative variables. For treatment failures/dropouts, the data that were collected during their stay in the study was included in the analysis. Only data for SAM (W/A < 70%) was extracted, with reference made to direction of whole group results

Sample size/power calculation: the study was planned to detect a 30% difference in the frequency and duration of diarrhoea of the two ORS. It was calculated that 82 children were needed per group to detect this difference with a power of 90% and a significance level of 5%. Previous data (frequency of 4.11 ± 2.67 stools/4 hours and duration of diarrhoea 36 ± 20.0 8 hours) from the Diarrhoea Treatment and Training Unit of 70 non-cholera children treated on WHO-ORS was used to determine the sample size. SAM is a subgroup (less than half of the total sample) and analysis is unlikely to be powered

Attrition/dropout for total sample: numbers reported, but details omitted. Four cases had a frequency of $^{3}10$ (meaning unclear) in last 24 hours and were considered treatment failure, six cases required more than the pre-determined volume of ORS, one case had dehydration phase of > 72 hours, one case needed > 150 ml/kg i.v. fluids and 12 cases (7%) of treatment failures on H-ORS were moved to WHO-ORS

General comments

Generalisability: SAM defined using a NCHS criteria of < 70% W/H; however, only W/A is reported in all tables. It is unclear whether or not the participants are severely malnourished as per WHO criteria (< 70% W/H), although in SAM group mean W/A is well below the 70% benchmark (~ 55%). SAM subgroup represents less than half of the total sample (47% H-ORS; 49% WHO-ORS) and children around 2 years of age with dehydration and with/without cholera diarrhoea

Outcome measures: appear to be suitable and appropriate

Intercentre variability: not applicable, one centre only

Conflict of interest: none

Details of intervention and control

WHO-ORS and H-ORS packets prepared in the departmental research lab

	H-ORS	WHO-ORS
Component, g		
NaCl	2.6	3.5
KCl	1.5	1.5
Trisodium citrate	2.9	2.9
Glucose	13.5	20
Concentration of, mmol/l		
Sodium	75	90
Potassium	20	20
Chloride	65	80
Citrate	10	10
Glucose	75	111
Osmolarity, mosmol/l:	245	311

NR, not reported.
a Significantly less in those receiving H-ORS.
b Reported as $p = 0.32$, but as this is not significant it would appear to be an error and should probably read $p = 0.032$.
c H-ORS, $n = 22$; WHO-ORS, $n = 19$.
d H-ORS, $n = 4$; WHO-ORS, $n = 7$.
e No key provided by authors.

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.
The data extraction is based on the SAM subgroup only, but the quality assessment is based on the total population of the RCT.

Alam *et al*. 2003[50]

Data extraction table

Reference and design	Intervention	Participants	Outcome measures
Author: Alam *et al.*[50] *Year:* 2003 *Country:* Bangladesh *Study design:* double-blind RCT *Setting:* inpatient [Clinical Research and Service Centre of International Centre for Diarrhoea, Disease Research (ICDDR), Bangladesh: Centre for Health and Population Research] *Number of centres:* one *Funding:* grant from WHO (no. C6/181/377)	*Intervention:* oral ReSoMaL (see end of table for details) *Control:* standard WHO-ORS (see end of table for details) Fluid deficit was corrected with 10 ml/kg/hour of the assigned ORS given over the first 2 hours, followed by 5 ml/kg/hour over a period of 10–12 hours until the deficit was corrected (dehydration was categorised according to the modified WHO guidelines). Ongoing stool losses were corrected with 5–10 ml/kg after each watery or loose stool. In patients with high purging rates, fluid intake was adjusted according to the ongoing stool output. ORS therapy was continued until diarrhoea ceased *Other interventions used:* pneumonia cases received i.m. or i.v. ceftriaxone 75 mg/kg/day once daily for 5 days and gentamicin 5 mg/kg/day in two divided doses. Other infections, complications, nutritional therapy or aspects of case management were provided consistent with the WHO guidelines All children were treated following the protocol of the WHO manual for the standardised treatment of SAM children and received acute and rehabilitation phase treatment until discharged. Children remained in the study until diarrhoea resolved, with subsequent transfer to a nutritional rehabilitation unit or home-based nutritional follow-up programme of the Clinical Research and Service Centre	*Definition of SAM:* W/L < 70% of the NCHS median or with bilateral pedal oedema *Number of participants:* $n = 130$ (ReSoMaL $n = 65$; WHO-ORS $n = 65$) *Sample attrition/dropout:* $n = 12$. ReSoMaL: $n = 7$ (three severe dehydration requiring i.v.'s, one symptomatic hypokalaemia, one severe hyperkalaemia; one severe pneumonia and one symptomatic hyponatraemia with seizure). WHO-ORS: $n = 5$ (one symptomatic hypokalaemia, one severe dehydration, one severe pneumonia and two parental withdrawal) *Sample crossovers:* none reported Children requiring i.v. fluid therapy for severe dehydration, septic shock or convulsion, children with concomitant illness requiring more intensive care, cases with severe hyperkalaemia (serum potassium ≥ 6.0 mmol/l), cases with severe hypokalaemia (serum potassium ≤ 1.5 mmol/l with or without symptoms or < 2.5 mmol/l with symptoms) and cases with severe hyponatraemia (serum sodium < 120 mmol/l with symptoms or < 115 mmol/l with or without symptoms) were withdrawn from the study *Inclusion criteria:* ■ children aged 6–36 months (either sex) with history of watery diarrhoea for ≤ 10 days and SAM (< 70% of the NCHS median or with bilateral pedal oedema) *Exclusion criteria:* ■ bloody diarrhoea, severe dehydration requiring i.v. fluids ■ signs of severe infection (i.e. severe pneumonia, sepsis, meningitis) *General characteristics of participants:* children aged 6–26 months with history of watery diarrhoea, and with or without cholera	*Primary outcomes:* number of children developing over-hydration and number of children with correction of basal hypokalaemia after 24 and 48 hours of treatment *Secondary outcome:* number of children remaining hyponatraemic at 24 and 48 hours of treatment *Method of assessing outcomes:* ■ laboratory tests on admission included blood tests (haematocrit, total and differential white blood cell count, serum protein and albumin); serum electrolytes (also at 24 and 48 hours); stool microscopy for leucocytes, red blood cells and parasites (including *Giardia lamblia, Entamoeba histolytica* and *Cryptosporidium*); stool culture for *Salmonella, Shigella* and *Vibrio;* stool culture for rotavirus by enzyme-linked immunosorbent assay ■ tests for diarrheagenic *Escherichia coli* were not performed If clinically indicated, urine for microscopy and culture and chest radiograph ■ Children were placed on a cholera cot and a paediatric urine collector was applied to collect urine separately ■ Stool weight, supplemented food and body weight were measured with an electronic scale (Sartorius, Göttingen, Germany) with a precision of 1.0 g ■ All intakes (ORS solutions, plain water and food) and outputs (stool, urine and vomitus) were quantified every 6 hours

- Body weight, vital signs (pulse, temperature and respiration) and other evidence of overhydration (i.e. puffy face, pedal oedema, respiratory hurry/distress) were recorded every 6 hours
- Overhydration was defined as > 5% weight gain after correction of dehydration at any time during the study period with any of the following signs: periorbital oedema/puffy face, increased heart rate (> 160/minute), or increased respiration (> 60/minute)
- Hypokalaemia was defined as serum potassium < 3.5 mmol/l, hyperkalaemia as serum potassium > 5.5 mmol/l, hyponatraemia as serum sodium < 130 mmol/l, and hypernatraemia as serum sodium > 150 mmol/l
- Duration of diarrhoea was calculated as the time in hours from the time of randomisation to the last watery stool followed by two consecutive soft/formed stools or no stool for 12 hours

Adverse symptoms: hyponatraemia

Length of follow-up: none reported, but states all children remained in the study until diarrhoea resolved

Recruitment dates: February 1998 to January 2000

Characteristics of participants

Characteristic	ReSoMaL (*n* = 65)	WHO-ORS (*n* = 65)	*p*-value
Mean age, months (SD)	15 (7)	15 (6)	NR
Sex, *n* (M : F)	39 : 26	42 : 23	NR
Mean body weight, kg (SD)	5.22 (0.92)	5.26 (0.95)	NR
Mean W/A % of NCHS median (SD)	50 (7)	51 (7)	NR
Mean WAZ (SD)	–4.7 (1)	–4.6 (0.7)	NR
Mean W/L % of NCHS median (SD)	66 (4)	66 (3)	NR
Mean WLZ (SD)	–3.6 (0.6)	–3.5 (0.5)	NR
Breastfed, *n* (yes : no)	45 : 21	47 : 17	NR
Mean duration of diarrhoea before admission, hours (SD)	77 (62)	74 (59)	NR
Mean number of stools in 24 hours before admission (SD)	12.5 (5)	14 (9)	NR
Dehydration status, *n* (none : some)	21 : 45	23 : 42	NR
Oedema present, *n* (%)	15/65 (23)	14/65 (22)	NR

Stool pathogen, *n* (%)			NR
Vibrio cholerae	18/65 (28)	19/65 (29)	
Shigella	5/65 (8)	2/65 (3)	
Salmonella	2/65 (3)	0/65	
Other *Vibrio*	3/65 (5)	5/65 (8)	
Rotavirus	10/65 (15)	12/65 (18)	

Results

Primary outcomes	**ReSoMaL (*n*=65)**	**WHO-ORS (*n*=65)**	***p*-value; OR (95% CI)**
Children adequately rehydrated at 12 hours, *n/N* (%)	45/59 (76)	51/63 (81)	*p*=0.68; OR 0.16 (95% CI 0.29 to 1.96)
Overhydration, *n/N* (%)	3/65 (5)	8/65 (12)	*p*=0.20; OR 0.3 (95% CI 0.1 to 1.5)
Basal hypokalaemia (potassium <3.5 mmol/l), *n/N* (%)	39/65 (60)	44/65 (68)	*p*=0.47; OR 0.7 (95% CI 0.3 to 1.6)
Hypokalaemia corrected at 24 hours, *n/N* (%)	14/38 (36)	2/44 (5)	*p*=0.0006; OR 12.3 (95% CI 2.4 to 117)
Hypokalaemia corrected at 48 hours, *n/N* (%)	18/38 (47)	7/44 (16)	*p*=0.004; OR 1.5 (95% CI 1.5 to 15.6)

Secondary outcomes	**ReSoMaL (*n*=65)**	**WHO-ORS (*n*=65)**	***p*-value; OR (95% CI)**
Mean serum potassium, mmol/l (SD)			
0 hours	3.03 (1)	3.3 (1)	*p*=0.7; OR <0.08 (–0.3 to 0.4)[a]
24 hours	4.0 (1)	3.2 (0.7)	*p*=0.01; OR (0.49 to 1.1)[a,b]
48 hours	4.6 (0.8)	3.4 (0.8)	*p*=0.01; OR 1.2 (0.3 to 1.0)[a]
Hyponatraemia (serum sodium <130 mmol/l), *n/N* (%)			
0 hours	25/65 (38)	19/65 (29)	*p*=0.35; OR 1.5 (0.7 to 3.4)
24 hours	24/62 (39)	15/64 (23)	*p*=0.9; OR 2.1 (0.9 to 4.8)
48 hours	17/59 (29)	6/60 (10)	*p*=0.017; OR 3.6 (1.2 to 12.2)
Severe hyponatraemia (serum sodium ≤120 mmol/l), *n/N* (%)			
0 hours	0/65	1/65 (2)	*p*=1.0; OR 0 (0 to 39)
24 hours	3/62 (5)	1/64 (2)	*p*=0.36; OR 3.2 (0.3 to 171)
48 hours	0	0	
Mean serum sodium, mmol/l (SD)			
0 hours	132.1 (6)	132.9 (8)	*p*=0.51; OR –0.8 (–3.3 to 1.7)[a]
24 hours	130.5 (6)	133.3 (6)	*p*=0.01; OR–2.8 (–4.9 to 0.7)[a]
48 hours	132.1 (4)	134.5 (4)	*p*=0.001; OR–2.4 (–3.9 to–1.0)[a]

Comments: three new cases of severe hyponatraemia developed in the ReSoMaL group. Although not explicitly stated, presumably no new case developed in the WHO-ORS group. Stool output, urine output, ORS intake, water intake, calorie intake from supplemented food and duration of diarrhoea and weight gain before discharge reported similar between groups, but no data shown

Other:	**Non-cholera diarrhoea**			**Cholera diarrhoea**		
hyponatraemia (serum <130 mmol)	**ReSoMaL (*n*=47)**	**Standard (*n*=46)**	***p*-value; OR (95% CI)**	**ReSoMaL (*n*=18)**	**Standard *n*=19**	***p*-value: OR (95% CI)**
0 hours, *n/N* (%)	13/47 (28)	11/46 (24)	NS; OR 1.2 (0.4 to 3.5)	12/18 (67)	9/19 (47)	NS; OR 2.2 (0.5 to 10)
24 hours, *n/N* (%)	11/47 (23)	7/46 (15)	NS; OR 1.7 (0.5 to 5.8)	13/18 (72)	8/19 (42)	NS; OR 3.6 (0.8 to 18)
48 hours, *n/N* (%)	7/47 (15)	4/46 (9)	NS; OR 1.84 (0.4 to 8.2)	10/11 (56)	2/19 (11)	NS; OR 10.63 (1.6 to 92.1)

Safety: the child in the ReSoMal group who was withdrawn owing to hyponatraemia with associated seizure was reported as having had a high purging rate (18 g/kg/hour) during the first 24-hour period

Convulsions: *n*=1 ReSoMaL (case did not have cholera). The study authors believed that the occurrence of the convulsion in the ReSoMal group should limit the use of ReSoMal in its current formulation in severely malnourished children with diarrhoea

Death: *n*=0

HIV: reported

Barriers to implementation

NR

Methodological comments

Allocation to treatment groups: cases were allocated using serially numbered, sealed envelopes supplied to the pharmacist of ICDDR

Blinding: states double-blind controlled study, with children assigned on enrolment thorough randomisation list (prepared by the WHO) following a permuted table of variable length. Pharmacist prepared the ORS in a clean bottle marked only with the child's name and study number according to list inside the serially numbered envelopes. The ORS solutions were reported to look identical and a code in the form of A and B was provided to the investigators for analysis. The group identity was disclosed for preparation of the final report, after preparation of data analysis tables

Comparability of treatment groups: states that baseline clinical characteristics such as age, body weight, W/A, W/L, breastfeeding status, oedematous state and dehydration status were comparable between the groups (*p*-values NR)

Method of data analysis: Student's *t*-test for comparison between groups of continuous variables for non-continuous variables; the chi-squared test/Fisher's exact test, using SPSS/PC+. For withdrawals, data collected until the time of withdrawal were included in the analysis

Sample size/power calculation: based on an expected reduction of persistence of hypokalaemia from 33% with standard WHO-ORS to 12% with ReSoMaL. Sample size was calculated to be 65 in each group (5% level of significance, 80% power and 10% dropout). Authors state that no reliable data exist on the development of overhydration quantified objectively. A sample size of 52 in each group was estimated, assuming a 20% difference in the development of overhydration between the groups (25% of WHO-ORS group and 5% of ReSoMaL group considered to develop overhydration, with a 5% level of significance, 80% power and 10% dropout). A subgroup analysis for hyponatraemia excluded children with cholera and is unlikely to be powered

Attrition/dropout: numbers and reasons reported. Children withdrawn from the study were followed and final outcome recorded

General comments

Generalisability: SAM defined using criteria of < 70% of the NCHS median W/L, which is in agreement with the WHO criteria for SAM

Outcome measures: appear to be suitable and appropriate. Outcomes are defined where necessary

Intercentre variability: not applicable, one centre only

Conflict of interest: NR, but staff from WHO reviewed protocol and supplied the ReSoMaL

Details of intervention and control

Composition of ReSoMaL and standard ORS

	ReSoMaL	Standard ORS
Concentration of, mmol/l		
Sodium	45	90
Potassium	40	20
Chloride	76	80
Citrate	7	10
Glucose	125	111
Magnesium	6	
Concentration of, µmol/l		
Zinc	300	
Copper	45	
Osmolarity, mosmol/l	300	311

NR, not reported; NS, not statistically significant; WAZ, weight-for-age *z*-score; WHZ, weight-for-height *z*-score.
a Difference between means (95% CI).
b OR at 24 hours not presented in the paper.
Note: although standard WHO-ORS does not contain magnesium, zinc or calcium, the WHO-ORS group did receive supplements as part of the centres' routine treatment of SAM.

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.

Alam *et al*. 2009[57]

Data extraction table

Reference and design	Intervention	Participants	Outcome measures
Author: Alam *et al.*[57] *Year:* 2009 *Country:* Bangladesh *Study design:* RCT *Setting:* inpatient (Dhaka hospital of the ICDDR followed by nutrition rehabilitation unit) *Number of centres:* one *Funding:* Nestlé Foundation and ICDDR, Bangladesh	*Intervention 1:* glucose-ORS *Intervention 2:* glucose-ORS + ARS *Intervention 3*: rice-ORS ORS had the same salt composition, but different substrates (see table at end for further details) Children with some dehydration were randomised to receive the assigned ORS within 1 hour, and those with severe dehydration within 6 hours of admission after i.v. rehydration. ORS given on hospital ward and continued until cessation of diarrhoea (acute phase) Other interventions used: i.v rehydration of severe dehydration, antibiotics where appropriate, erythromycin for cholera, vitamin A, folic acid and other multivitamin supplements, glucose solution for hypoglycaemic children, breastfeeding continued ad libitum, supplementary feeding with F100 diet, semi-solid food for older children. Further details at end of paper	*Definition of SAM:* W/L < 70% of NCHS median or with bipedal oedema *Number of participants:* 316 screened, 175 randomised (glucose-ORS *n* = 58, glucose-ORS + ARS *n* = 59, rice-ORS *n* = 58) *Sample attrition/dropout:* 170 (97%) completed acute phase (five withdrew consent: one glucose-ORS, three glucose-ORS + ARS, one rice-ORS). 137 (78%) completed convalescent phase (42 glucose-ORS, 50 glucose-ORS + ARS, 45 rice-ORS) – reasons not given for convalescent dropouts *Sample crossovers:* none reported *Inclusion criteria:* SAM children of either sex, aged 6–60 months, acute watery diarrhoea < 48 hours duration and stool dark-field microscopy demonstrating presence of cholera. Those with hypoglycaemia, hypothermia, hyponatraemia, dehydration and other associated-infections were also eligible *Exclusion criteria:* dysentery (blood in stool), severe infections (severe pneumonia, clinical sepsis, meningitis) *General characteristics of participants:* SAM children aged 6–60 months with acute watery diarrhoea and cholera	*Primary outcomes:* ■ stool output *Secondary outcomes:* ■ days to attain oedema-free W/L of 80% (of NCHS median) ■ diarrhoea duration ■ weight gain ■ fluid losses (urine and vomit output) ■ fluid intake (ORS, water and milk) ■ recovery *Method of assessing outcomes:* study eligibility confirmed by physical examination, blood, stool and urine samples 'Some dehydration' defined as presence of ≥ 2 signs or symptoms (irritable/less active,* sunken eyes, dry mucosa, thirst, reduced skin turgor*) with at least one sign marked by* 'Severe dehydration' defined as the presence of signs of 'some dehydration' plus at least one key sign (lethargy/coma,* inability to drink, but not refusal to drink,* uncountable/absent radial pulse*) Therapeutic failure defined as continuation of diarrhoea beyond seventh day of randomisation Unscheduled i.v. therapy defined as requirement of i.v. fluid any time after randomisation owing to appearance of signs of severe dehydration, excessive vomiting preventing adequate ORS intake or dehydration signs lasting > 6 hours Hypokalaemia = serum potassium < 3.5 mmol/l; severe hypokalaemia = serum potassium < 1.5 mmol/l; hyperkalaemia = serum potassium > 6.0 mmol/l; hyponatraemia = serum sodium < 130 mmol/l; severe hyponatraemia = serum sodium 115 mmol/l; hypernatraemia = serum sodium > 150 mmol/l Acute illness = diarrhoea phase; convalescent phase = after resolution of diarrhoea and until oedema-free W/L of 80% attained

Children weighed on admission and placed on a cholera cot. Paediatric urine collector used to collect stools and urine separately. Body weight and weight of stools and supplemented foods weighed on an electronic scale (Sartorius) with gram precision. All intakes (ORS, water, i.v. fluids and foods) and outputs (stool, urine and vomit) measured for each 6-hour period in acute phase. Vital signs and dehydration and signs of overhydration monitored every 6 hours

Duration of diarrhoea calculated from time of randomisation to last watery stool

Adverse symptoms: none reported

Length of follow-up: ORS continued until cessation of diarrhoea (the last watery stool is followed by ≥2 soft/formed stools or no stool for 12 hours). After discharge, children followed-up at home weekly for at least 6 weeks (these data are not presented in this paper)

Standard treatment lasted through a convalescent phase until 80% W/L reached

Recruitment dates: July 2001 to December 2004

Characteristics of participants

Characteristic	Glucose-ORS (*n* = 58)	Glucose-ORS + ARS (*n* = 59)	Rice-ORS (*n* = 58)	*p*-value
Age, months	27.17 ± 12.36	28.36 ± 13.42	27.33 ± 11.97	0.858
Sex M : F	26 : 32	34 : 25	32 : 26	0.357
Weight, kg	6.90 ± 1.32	7.09 ± 1.52	6.78 ± 1.43	0.513
Length, cm	76.84 ± 7.11	77.34 ± 8.31	76.54 ± 8.15	NR
W/A (% of NCHS median)	54.51 ± 9.50	53.42 ± 6.86	53.16 ± 7.94	0.645
W/L (% of NCHS median)	68.99 ± 4.92	69.01 ± 5.27	67.54 ± 6.19	0.257
WAZ	–4.38 ± 68[a]	–4.31 ± 0.63	–4.39 ± 0.71	0.793
WLZ	–3.14 ± 1.88	–2.76 ± 46[a]	–3.38 ± 0.60	0.185
MUAC, mm	112.7 ± 9.9	113.6 ± 9.7	111.9 ± 10.8	0.678
MUAC with < 110 mm, *n* (%)	19 (33)	18 (31)	23 (39)	0.70
Diarrhoea duration before admission, hours	12.59 ± 8.27	13.07 ± 9.11	10.98 ± 5.73	0.326
Stools in last 24 hours before admission, *n*	14.36 ± 6.00	14.02 ± 6.09	14.55 ± 7.16	0.901
Vomiting duration before admission, hours	11.29 ± 8.01	11.31 ± 8.28	10.16 ± 4.7	0.613
Vomiting in last 24 hours, *n*	10.12 ± 6.93	11.83 ± 8.03[b]	12.28 ± 7.67[c]	0.271

Breastfed at illness onset, *n* (%)	32 (55)	18 (31)	29 (50)	0.018
Severe dehydration at admission, *n* (%)	48 (84)	49 (83)	49 (84)	0.971
Pedal oedema, *n* (%)	47 (81)	48 (81)	40 (69)	0.193
Hypothermia, *n* (%)[d]	12 (20)	7 (12)	11 (19)	0.405
Have received i.v. fluids, *n* (%)	50 (86)	50 (86)	49 (84)	0.961
Hyponatraemia, *n* (%)	10 (17)	14 (24)	14 (24)	0.599
Hypokalaemia, *n* (%)	23 (40)	14 (24)	20 (34)	0.170
Hypoglycaemia, *n* (%)	2 (4)	4 (7)	8 (14)	0.161

Comments: data are mean ±SD unless stated otherwise

Baseline characteristics were comparable between the three groups, except for breastfeeding; paper reports this was less frequent in glucose-ORS group, but data indicate lower frequency in the glucose-ORS + ARS group. 147/175 (84%) were clinically assessed to have severe dehydration in agreement with their mean weight gain of 11.4% (95% CI 10.4 to 12.5) at resolution of diarrhoea. Approximately one-third were acutely malnourished as indicated by MUAC < 110 mm; other risks of death included pedal oedema (77%) and hypothermia (17%). Hypernatraemia or severe hyponatraemia was not observed in any child. The paper reports other baseline characteristics including sociodemographic characteristics, serum concentrations of electrolytes and Hb, but these have not been extracted

Results

Primary outcomes	**Glucose-ORS (*n* = 58)**	**Glucose-ORS + ARS (*n* = 59)**	**Rice-ORS (*n* = 58)**	***p*-value (95% CI)**
Stool output, ml/kg				
At 24 hours	355	309	236	0.004, difference 109 (44 to 174), 32% reduction[e]
At 48 hours	600	518	382	0.007, difference 213 (79 to 346), 37% reduction[e]
At 72 hours	735	645	475	0.018, difference 242 (73 to 412), 36% reduction[e]

Comments: Data are mean per cent of initial body weight. The 72-hour results (and 24- and 48-hours results for stool output) reported here for individual study groups are estimated by reviewer from bar charts. SE presented, but not data extracted. The paper presents results for every 6-hourly period up to 72 hours, but these have not been data extracted. Statistical difference was entirely contributed by the rice-ORS group. The trend towards reduction of stool output in glucose-ORS + ARS group vs glucose-ORS group was NS

Secondary outcomes	**Glucose ORS (*n* = 58)**	**Glucose-ORS + ARS (*n* = 59)**	**Rice-ORS (*n* = 58)**	***p*-value**
Weight gain at 72 hours, % initial weight	11	9.7	13	0.05
Median diarrhoea duration, hours (95% CI)	72 (62 to 82)	60 (50 to 70)	54 (44 to 54)	0.530
Days to attain 80% of median W/L, mean ± SD	7.14 ± 2.26	7.12 ± 2.2	7.2 ± 3.78	0.99
Vomit output at 72 hours, ml/kg	30	37	33	NR/NS
Urine output at 72 hours, ml/kg	184	186	177	NR/NS
ORS intake at 72 hours, ml/kg	710	620	450	0.012, 38% reduction[f]
Water intake at 72 hours, ml/kg	215	230	260	0.03[g]
Milk formula intake at 72 hours, ml/kg	329	333	346	NR/NS

Required unscheduled i.v. therapy, *n* (%)	10/56 (18)	11/59 (19)	6/57 (11)	0.858
Therapeutic failure, *n* (%)	2 (3.6)	1 (1.8)	2 (3.6)	0.785
Deaths, *n*	0	0	0	NR

Comments: outcomes reporting results at 72 hours are estimated by reviewer from bar charts. The paper presents results for every 6-hourly period up to 72 hours, but these have not been data extracted. Significant differences in weight gain, ORS intake and water intake were entirely accounted for by the rice-ORS group, according to the least significant difference post hoc analysis. Overall mean weight gain at 72 hours was 114 g/kg (95% CI 103 to 124 g/kg). Overall mean duration of diarrhoea was 66 hours (95% CI 62 to 71 hours) with an overall median duration of 60 hours (95% CI 54 to 66 hours). Diarrhoea duration compared by log-rank test, df = 2, log-rank = 1.27. A survival plot for recovery from diarrhoea after inclusion was also presented for 167 children, but has not been data extracted. No statistical difference was observed between groups (log-rank = 1.27, df = 2, statistical value = 0.53)

Safety: during the acute phase of treatment, no children developed features of overhydration, cardiac failure, hypoglycaemia, severe hypo- or hyperkalaemia or severe hypo- or hypernatraemia

HIV: none reported

Barriers to implementation

None reported

Methodological comments

Allocation to treatment groups: randomisation using consecutive sealed envelopes. A statistician not involved in the study prepared the randomisation list and sequentially numbered sealed envelopes containing a slip of paper identifying the allocated ORS. The list was retained by the hospital pharmacist who prepared the ORS in bottles marked with the patient's name and study number

Blinding: states that treatment could not be blinded to the people involved in the study (assume this refers to patients and care providers alike) because of visible differences in the ORS solutions. No details regarding blinding of outcome assessors

Comparability of treatment groups: baseline characteristics were comparable between the three groups (*p*-values reported), except for breastfeeding – paper reports this was less frequent in glucose-ORS group, but data indicate lower frequency in the glucose-ORS + ARS group

Method of data analysis: not ITT analysis. The five children withdrawn from the study by their parents were not included in the analysis. States that the baseline characteristics of these children did not differ from the remainder of the included children. Fewer children were analysed at the end of the convalescent phase than the acute phase. Baseline characteristics and outcomes were compared using one-way ANOVA followed by a post hoc least significant difference test, and a non-parametric Kruskal–Wallis test was used for the continuous variables. Chi-squared test used for comparison of categorical variables and Fisher's exact test was applied when appropriate. Kaplan–Meier survival analysis was performed for comparing diarrhoea duration

Sample size/power calculation: Authors state that sample size was not calculated to detect a significant difference in death rates owing to ethical and statistical reasons (requirement of huge sample size). Instead, sample size was calculated to detect a 30% reduction in stool output in first 24 hours of treatment with either glucose-ORS + ARS or rice-ORS. This level of stool output reduction was based on results of an unpublished pilot study in similar children having mean stool weight (± SD) of 158 g (± 95) and of published data in adults. This required a sample size of 63 per group for a two-sided alpha-level of < 0.05 and a beta-level of 0.2

Attrition/dropout: numbers and reasons reported for acute phase, but only numbers given for convalescent phase. 170 (97%) completed acute phase (five withdrew: one glucose-ORS, three glucose-ORS + ARS and one rice-ORS). 137 (78%) completed convalescent phase (42 glucose-ORS, 50 glucose-ORS + ARS, and 45 rice-ORS)

General comments

Generalisability: likely that most of the children would meet the current WHO criteria (W/L < 70%, W/L *z*-score < –3 SD) given a mean of 68% and –3.09, respectively. Age ranged from 6 to 60 months but mean age 27 months, therefore, it is likely to be representative of infants and toddlers. All had cholera and some had comorbidities (e.g. electrolyte disturbances)

Outcome measures: outcomes were appropriate

Intercentre variability: N/A

Conflict of interest: funded by Nestlé Foundation and ICDDR. No conflicts of interest reported

Standard management

After randomisation, all children were treated as per the standard ICDDRB protocol for management of severely malnourished children

- Children without an apparent extraintestinal infection received 100 mg/kg parenteral ampicillin and 5 mg/kg gentamicin in four and two divided doses, respectively, for 5 days
- All received 12.5 mg/kg erythromycin every 6 hours for 3 days for cholera
- Those with oral candidiasis received 100,000 units nystatin oral suspension every 6 hours until resolution of condition
- All received oral vitamin A: 200,000 IU for those without xerophthalmia and > 1 year, 100,000 IU for those aged 6–12 months, for those with xerophthalmia > 1 year 200,000 IU on admission and on following day and again at discharge and children < 1 year received same schedule, but half the dose
- All children received 1.25 mg folic acid and 2 mg/kg elemental zinc daily for 15 days
- All received multivitamin supplements (composition reported but not data extracted) twice daily for 15 days if > 1 year, or half dose if < 1year
- Children with hypoglycaemia or blood glucose < 3 mmol/l were fed 50 ml of 10% glucose solution orally or by nasogastric tube; those with symptomatic hypoglycaemia received 2 ml/kg of 25% glucose solution i.v.
- Breastfeeding continued ad libitum
- Supplementary feeding with a F100 diet (100 kcal/100 ml) given in an amount of 10 ml/kg (10 kcal/kg) for each feed every 2 hours on the first day. This was gradually increased to deliver 150 kcal/kg/day for the next 7 days according to needs. If the child was reluctant to feed or weak or with painful mouth sores, food was administered via a nasogastric tube until the child could take it orally
- Semi-solid food (cooked rice, lentils and vegetables) were given to older children during the convalescence and rehabilitation phase in addition to F100

Rehydration

- Children with severe dehydration were initially rehydrated using i.v. 'cholera saline' containing sodium 133, potassium 13, chlorine 98 and acetate 48 (all mmol/l) until their recovery from shock or severe dehydration
- Children with some dehydration on admission or following i.v. rehydration, the estimated fluid deficit was corrected with one of the assigned ORSs, 100 ml/kg for 6 hours. Additionally, after each watery stool, 5–10 ml/kg of the same ORS was used for matching ongoing stool losses
- Children with some dehydration were randomised to receive the assigned ORS within 1 hour, and those with severe dehydration within 6 hours of admission after i.v. rehydration

Composition of ORS (differed only in glucose, ARS and rice composition)

- ORS given on hospital ward and continued until cessation of diarrhoea (acute phase)
- After resolution of diarrhoea, children were transferred to the hospital nutritional rehabilitation unit until oedema-free W/L 80% attained
- Following this, children were discharged from hospital and followed up in their home weekly for at least 6 weeks

Ingredient	Glucose-ORS	Glucose ORS + ARS	Rice-ORS
Glucose, mmol/l	90	90	0
Rice powder, g/l	0	0	50
Amylase-resistant starch, g/l	0	50	0
Sodium, mmol/l	75	75	75
Potassium, mmol/l	40	40	40
Chloride, mmol/l	87	87	87
Citrate, mmol/l	10	10	10
Magnesium, mmol/l	3	3	3
Zinc, µmol/l	300	300	300
Copper, µmol/l	45	45	45
Calculated osmolarity, mosmol/l	305	305	215

ANOVA, analysis of variance; Hb, haemoglobin; ICDDRB, International Centre for Diarrhoeal Disease Research, Bangladesh; IU, international units; N/A, not applicable; NR, not reported; NS, not statistically significant; WAZ, weight-for-age z-score; WHZ, weight-for-height z-score..

a Possible errors.

b Paper reports a second figure of 11.83 ± 8.03, but appears to be a typeset error.

c Paper reports a second figure 12.28 ± 7.67, but appears to be a typeset error.

d Rectal temperature ≤ 36 °C. *p*-values based on one-way analysis of variance or chi-squared or Fisher's exact test as appropriate.

e Compared with glucose-ORS group; difference between rice-ORS and glucose-ORS groups reported in paper (i.e. not estimated by reviewer).

f Significantly lower in rice-ORS group compared with glucose-ORS group.

g Significantly greater in rice-ORS group.

The glucose-ORS is a modification of the WHO ReSoMaL ORS containing higher sodium (75 vs 45 mmol/l) to address the greater stool sodium loss in cholera diarrhoea. The rice-ORS is routinely used in hospitals and is prepared by mixing the salt mixture and rice powder in 1050 ml of water and boiling for 7–8 minutes.

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% ✓ of those randomised	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.

Dutta *et al.* 2000[55]

Data extraction table

Reference and design	Intervention	Participants	Outcome measures
Author: Dutta *et al.*[55] *Year:* 2000 *Country:* India *Study design:* double-blind, RCT *Setting:* inpatient (hospital) + community after discharge and until follow-up *Number of centres:* one *Funding:* not stated	*Intervention:* zinc-supplemented syrup (177 mg/day in three divided doses, 40 mg elemental zinc/day) *Control:* placebo syrup *Other interventions used:* all children received standard ORS initially plus standard feeding regimen (see end of table for details)	*Definition of SAM:* not specifically stated. Uses the IAP W/A classification system, though results are reported for all children (not separately by grade). Mean baseline MUAC is < 11 cm *Number of participants:* $n = 80$ (zinc: $n = 44$, control $n = 36$) *Sample attrition/dropout:* unclear (see *Methodological comments* on page 177) *Sample crossovers:* none *Inclusion criteria:* male children, aged 3–24 months, < 80% Harvard standard W/A, history of watery diarrhoea (more than four times within previous 24 hours) for ≤ 72 hours and clinical signs and symptoms of 'some' dehydration (e.g. sunken eyes, reduced skin elasticity, rapid pulse, dry mouth and thirst) *Exclusion criteria:* history of treatment with antibiotics, other systemic infections (e.g. septicaemia, meningitis, pneumonia, urinary tract infection, otitis media), chronic underlying diseases (TB, liver diseases), need for intensive care (i.e. life-support system, blood transfusion or total parenteral nutrition), exclusively breastfed *General characteristics of participants:* malnourished male children, aged 3–24 months, with acute dehydrating diarrhoea; majority have SAM (grade III or IV)	*Primary outcomes:* not specifically stated as primary, but appear to be: ■ recovery ■ diarrhoeal duration ■ diarrhoeal volume ■ ORS consumption Recovery defined as passage of normal stool or no stool for last 18 hours *Secondary outcomes:* ■ weight gain ■ gain in MUAC ■ height gain *Method of assessing outcomes:* weighed unclothed at same time every day using scales with a sensitivity of 20 g; nutritional status assessed using IAP classification; degree of dehydration assessed by the WHO criteria; stool samples collected in sterile MacCartney's bottles for detection of enteropathogens using 'standard methods'[92] Stool losses measured on pre-weighed disposable diapers; urine separated from stools using urine collection bags; vomitus weighed on pre-weighed gauze pads. All intake and output measured and recorded every 8 hours until diarrhoea stopped, withdrawal from study, or up to day 5 if child did not fulfil criteria of recovery *Adverse symptoms:* NR *Length of follow-up:* treatment until diarrhoea ceased or up to day 5. Additional follow-up up to 30 days (including up to 5 days hospitalisation) *Recruitment dates:* June 1997 to May 1998

Characteristics of participants

Characteristic	Zinc syrup (*n* = 44)	Placebo syrup (*n* = 36)	*p*-value
Mean age ± SD, months	10.4 ± 5.4	11.0 ± 4.9	
Mean body weight ± SD, kg	5.5 ± 1.6	5.8 ± 1.5	
Mean height ± SD, cm	65.5 ± 8.4	67.5 ± 6.9	
Mean MUAC ± SD, cm	10.3 ± 1.3	10.5 ± 1.0	
Nutritional status, *n* W/A (%)			
Grade I ≥ 80% of median	–	–	
Grade II 70% < 80% of median	6 (13)	6 (17)	
Grade III 60% < 70% of median	10 (23)	11 (30)	
Grade IV < 60% of median	28 (64)	19 (53)	
Diarrhoea before admission ± SD			
Mean duration, hours	33.4 ± 11.5	38.3 ± 10.3	
Frequency/24 hours	13.8 ± 3.8	13.3 ± 3.9	
Degree of dehydration	Some	Some	
Enteropathogens, *n* (%)			
Single pathogen	34 (77)	23 (64)	
Mixed pathogens	7 (16)	9 (25)	
No pathogen	3 (7)	4 (11)	

Comments: the study reports *n* (%) for specific single and mixed pathogens, but these have been summed by reviewer. Pathogens identified were: single pathogens – enteropathogenic *E. coli*, enteroaggregative *E. coli, Salmonella typhimurium, Shigella flexneri, Shigella sonnei, V. cholera* O1, *Clostridium difficile,* rotavirus, *V. cholera* non-O1 non-O139; mixed pathogens – EPEC + *S. typhimurium,* EPEC + rotavirus, EPEC + *S. flexneri,* rotavirus + *S. flexneri*, rotavirus + *S. typhyimurium*. No *p*-values were reported

Results

Primary outcomes	Zinc syrup (*n* = 44)	Placebo syrup (*n* = 36)	*p*-value
Patients recovered, *n* (%)[a]	44 (100)	32 (89)	0.04
Mean recovery ± SD, hour[b]	70.4 ± 10.0	103.4 ± 17.1	0.0001
Total liquid stool output, kg	1.5 ± 0.7	2.4 ± 0.7	0.0001
Total liquid, ml (liquid food + water)	867.0 ± 466.1	1354.7 ± 675.6	0.0001
Consumption of total ORS, litres	2.5 ± 1.0	3.6 ± 0.8	0.0001

Comments: assumed that total stool output, total liquid and consumption of ORS were calculated to recovery or up to day 5

Secondary outcomes	Zinc syrup (*n* = 44)	Placebo syrup (*n* = 36)	*p*-value
Per cent weight gain on recovery (% admission weight) ± SD	3.9 ± 4.1	3.2 ± 2.9	0.41
Per cent weight gain on 30th day (% recovery weight) ± SD	2.6 ± 3.3[c]	2.9 ± 3.7[d]	0.88
Per cent gain in mid-arm circumference on 30th day (% recovery MAC) ± SD	5.2 ± 3.4[c]	3.4 ± 2.3[d]	0.08
Per cent gain in height on 30th day (% recovery height) ± SD	1.1 ± 0.9[c]	0.6 ± 0.5[d]	0.06

Comments: in subgroup analysis of different nutritional status, the duration of diarrhoea, stool output, consumption of ORS and other fluids were significantly less in the zinc-supplemented group than in the placebo group (numerical data not presented in the paper)

Safety: NR

HIV: NR

Barriers to implementation

NR

Methodological comments

Allocation to treatment groups: randomised using a random numbers table and patients were allocated a specific-numbered bottle of either zinc or placebo syrup

Blinding: double blind. The taste, colour and consistency of the zinc and placebo syrups were identical, as were the bottles that were numbered. The person who made the randomisation was not associated with the study. The serial code numbers were kept in a sealed envelope with a senior officer who identified the groups after the study completion

Comparability of treatment groups: paper states that groups were comparable for baseline characteristics, although no *p*-values were reported. Note that the zinc status of the participants was not assessed, so it is not known whether children were zinc deficient or whether or not this was comparable between the groups

Method of data analysis: appears to be ITT analysis for primary outcomes and also weight gain at recovery. The other secondary outcomes were analysed on a proportion of patients. Comparability of the study and control groups according to patient characteristics, and differences in proportion of cured patients in the two groups, were determined using chi-squared tests. Means of outcome variables of the two groups were compared by applying Student's *t*-test

Sample size/power calculation: NR

Attrition/dropout: does not specifically report any dropouts, but outcomes at 30-days follow-up are only presented for 18 and 16 patients in the zinc and placebo groups, respectively. Thus, can possibly assume 26 and 20 patients, respectively, dropped out/withdrew by this time point

General comments

Generalisability: young infants (aged 3–24 months) and males only. Definition of SAM is not provided and it is unclear whether or not the children would meet the current WHO criteria as only 59% (47/80) of population are < 60% Harvard standard W/A, but the majority have a MUAC < 11 cm

Outcome measures: outcomes were appropriate, although mortality was not a specified outcome (no deaths reported)

Intercentre variability: N/A

Conflict of interest: funding not stated. Greenco Biologicals (Pvt) Ltd prepared the zinc syrup and placebo syrup

All children received standard ORS solution (mmol/l: sodium, 90; potassium, 20; citrate, 10; chloride, 80; glucose, 111) at the rate of 75–100 ml/kg body weight for first 4–6 hours of admission for correction of initial dehydration. If not achieved, the same solution was repeated for another 4–6 hours. When all the signs and symptoms of dehydration disappeared, ORS solution was given as maintenance therapy in amounts matching stool volume and loss in vomitus. However, more fluid was given if the child wanted it and if there were clinical indications. If any patient developed severe dehydration during the follow-up period, he received i.v. infusion of RL according to WHO guidelines

Zinc-supplemented syrup	Placebo syrup
177 mg/day in three divided doses, 40 mg elemental zinc/day. Each 5 ml of zinc syrup contained 59 mg of zinc sulphate	Identical in taste, consistency and colour to the zinc syrup

Immediately after rehydration, feeding was resumed in both groups. Breastfeeding was allowed as wanted. Non-breastfed children received half-strength milk for the first 24 hours, and the strength gradually increased until discharge. Older children were offered the standard hospital diet of rice, lentils and fish (cereal/vegetable diet) appropriate for their age

At the time of discharge, all the children were advised to continue the assigned bottle of syrup until it was finished. Mothers were advised to give at least one extra meal or liquid feed per day during the recovery period

N/A, not applicable; NR, not reported.
a Within 5 days of hospitalisation.
b Mean recovery time denotes duration of diarrhoea.
c Follow-up of 18 patients.
d Follow-up of 16 patients.

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% ✓[a] (primary outcomes)	60–79%	< 60% ✓[a] (secondary outcomes)	Cannot tell	
Summary of withdrawals and dropouts *(Methodological strength of study)*	*Strong* ✓[b]	*Moderate*	*Weak* ✓[a]		
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[b] (Overall methodological strength of study – based on sections A–F)	Strong	Moderate ✓	Weak		

N/A, not applicable.

a The percentage of participants completing the study varied according to outcomes – for the primary outcomes of recovery, diarrhoeal volume and duration and ORS consumption as well as weight gain on recovery – data appeared to be available for all participants. For secondary outcomes of gain in weight, mid-arm circumference and height on 30th day, data were available for ~ 42% of participants only. Therefore, have indicated both strong and weak ratings for this section.

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

Dutta *et al*. 2001[54]

Data extraction table

Reference and design	Intervention	Participants	Outcome measures
Author: Dutta *et al.*[54] *Year:* 2001 *Country:* India *Study design:* double-blind, RCT *Setting:* inpatient (hospital) *Number of centres:* one *Funding:* not stated	*Intervention:* H-ORS (224 mmol/l) *Control:* standard WHO/UNICEF ORS (311 mmol/l) All children were rehydrated orally within 4–6 hours using the assigned ORS solution. It was then given to replace continuing losses (liquid stool and vomitus) until diarrhoea stopped (two formed stools passed, or no stool for 12 hours) or for up to 5 days if diarrhoea persisted. Children, other than those who were very ill, were discharged on recovery *Other interventions used:* all children were allowed to drink water ad libitum, breastfeeding and formula/animal milk were permitted, older children received the normal diet, which they were used to before the illness. No drug therapy was given Composition of ORS at end of table	*Definition of SAM:* < 60% Harvard standard W/A (without oedema) *Number of participants:* $n = 64$ (H-ORS $n = 32$, standard ORS $n = 32$) Sample attrition/dropout: appears none (though NR) *Sample crossovers:* none *Inclusion criteria:* male children, aged 6–48 months, < 60% Harvard standard W/A without oedema, marasmic, history of watery diarrhoea (three or more loose, watery stools/day) for ≤ 72 hours and clinical signs and symptoms of 'some' dehydration (e.g. thirst or eagerness to drink, sunken eyes, dry mouth and tongue and loss of skin elasticity) *Exclusion criteria:* history of another episode of diarrhoea 1 month prior to onset of present illness, receipt of antibiotics or ORT during this episode of diarrhoea, obvious parenteral infection (septicaemia, meningitis, pneumonia, urinary tract infection), need for special medical care (i.e. life-support system, blood transfusion or total parenteral nutrition), exclusively breastfed, obvious signs of kwashiorkor *General characteristics of participants:* severely malnourished, marasmic, male children, aged 6–48 months, with dehydrating acute watery diarrhoea	*Primary outcomes:* not specifically stated *Outcomes:* ■ recovery ■ duration of diarrhoea ■ volume of diarrhoea (stool output) ■ ORS intake ■ fluid intake ■ weight gain ■ sodium and potassium concentrations Recovery not specifically defined, but assume is until diarrhoea stopped (two formed stools passed or no stool for 12 hours) *Method of assessing outcomes*: weighed unclothed at same time each day on a balance of 10 g precision; nutritional status assessed using IAP classification; stool samples examined using 'standard techniques'[92] for characterisation of bacterial isolates; detection of enteropathogens using microscopic examination (trophozoites and cysts of *Entamoeba histolytica* and *Giardia lamblia*), enzyme linked immunosorbent assay (ELISA) and polyacrylamide gel elecrophoresis (rotavirus) Serum Sodium and potassium estimated from blood samples Stool losses measured on pre-weighed disposable diapers; urine separated from stools using urine collection bags; vomitus weighed on pre-weighed gauze pads; measurement units sensitive to 1 g or 1 ml. Intake and output measured and recorded 8 hourly until diarrhoea stopped or for up to 5 days if it persisted *Adverse symptoms:* NR *Length of follow-up:* not specifically stated but treated until diarrhoea stopped or for up to 5 days *Recruitment dates:* July 1997 to August 1999

Characteristics of participants:

Characteristic	H-ORS (n-32)	Standard ORS (*n* = 32)	*p*-value
Age, months	17.3 (9.7)	22.5 (15.6)	
Weight on admission, kg	5.7 (1.7)	5.8 (1.6)	
W/A, *n* (%)			
60–69%	2 (6)	1 (3)	
< 60%	30 (94)	31 (97)	
Duration of diarrhoea before admission, days[a]	21.3 (8.2)	22 (8.0)	
Stool frequency/day	15 (3)	13 (4)	
Vomiting, *n* (%)	8 (25)	9 (28)	
Degree of dehydration:			
'Some' dehydration, *n* (%)	32 (100)	32 (100)	
Serum sodium, mmol/l	130.0 (3.3)	129.7 (3.1)	
Serum potassium, mmol/l	3.1 (0.3)	3.1 (0.3)	
Per cent weight loss	6.1 (2.2)	6.3 (2.1)	
Enteropathogens, *n* (%)			
Single pathogen	24 (75)	26 (81)	
Mixed pathogens	5 (16)	4 (13)	
No pathogens	3 (9)	2 (6)	

Comments: results are expressed as mean (SD) unless otherwise stated. The study reports *n* (%) for specific single and mixed pathogens, but these have been summed by reviewer. Pathogens identified were: enteropathogenic *E. coli*, rotavirus, *Vibrio cholerae, Shigella flexneri, Salmonella typhimurium, Giardia lamblia, Aeromonus* sp., *Klebsiella*. No *p*-values were reported

Results

Outcomes	H-ORS (*n* = 32)	Standard ORS (*n* = 32)	*p*-value
Patients recovered within 5 days, *n* (%)	32 (100)	29 (91)	> 0.05
Median survival time to recovery, hours	36	53	0.001
Duration of diarrhoea after initiation of therapy, hours	41.5 (25.1)	66.4 (32.3)	0.001
Stool output			
0–24 hours, g/kg	73.4 (23.1)	105.9 (44.6)	0.001
24–48 hours, g/kg	34.9 (13.5)	87.5 (66.5)	0.001
48–72 hours, g/kg	28.4 (18.0)	90.4 (67.7)	0.01
At recovery, g/kg/day	52.3 (21.3)	96.6 (42.8)	0.0001
ORS intake			
0–24 hours, ml/kg	109.7 (32.2)	184.5 (53.7)	0.0001
24–48 hours, ml/kg	73.4 (22.7)	151.2 (81.3)	0.0001
48–72 hours, ml/kg	54.9 (28.3)	151.5 (65.0)	0.001
At recovery, ml/kg/day	111.5 (39.4)	168.9 (52.4)	0.0001
Fluid intake (ORS + water + liquid food), ml/kg/day	214.6 (61.2)	278.3 (99.3)	0.003
Per cent of weight gain[b] (% of admission weight)	4.3 (1.2)	5.4 (1.3)	0.001

Comments: results are expressed as mean (SD) unless otherwise stated

- Increases in sodium and potassium in the two groups were the same; mean serum sodium and potassium concentrations at time of recovery or on day 5 for those who did not recover, were similar in both treatment groups (table presented in paper, but not extracted here)

Safety: none of the children in either group became overhydrated in the course of treatment

- Blood samples were drawn to measure hypernatraemia (serum sodium > 150 mmol/l) and hyponatraemia (serum sodium < 130 mmol/l) and hyperkalaemia (serum potassium > 5 mmol/l) and hypokalaemia (serum potassium < 3.5 mmol/l), but incidence was NR in the results, thus, assume this reflects some safety element

HIV: NR

Barriers to implementation

NR

Methodological comments

Allocation to treatment groups: a computer-generated randomisation table was used to allocate the different ORS packets. An individual not associated with the study provided the ORS packets

Blinding: double blind. The packets of ORS were similar in appearance and packaged in identical sachets. The randomisation table was held by an individual not associated with the study. Decoding was performed at the end of the study

Comparability of treatment groups: groups appear similar for baseline characteristics, although the mean age of children in the H-ORS group was slightly lower. The study reports characteristics are comparable although no *p*-values were reported

Method of data analysis: appears to be ITT analysis. Groups were compared using the chi-squared test. Means of the outcome variables of the two groups (time-specific stool output, intake of ORS, total fluid intake, weight gain or loss and electrolyte concentrations on recovery) were compared using the Student's *t*-test. The difference in proportions of cured patients between the two groups was examined using the chi-squared test. Recovery time of patients in the two groups was calculated using a survival analysis technique in accordance with the Kaplan–Meyer method

Sample size/power calculation: NR

Attrition/dropout: none reported, but may have occurred as study reports intake and output measuring took place but stopped if child was withdrawn from study

General comments

Generalisability: vast majority of children were SAM (61/64, 95%) based on W/A criteria (defined here as < 60% Harvard standard W/A); young children (aged 6–48 months), males only. As W/H and W/L is NR it is uncertain whether or not the study group meet the current WHO criteria. However, as they are described as marasmic, it is likely that they would

Outcome measures: outcomes appear appropriate, although mortality was not a specified outcome (no deaths are reported)

Intercentre variability: N/A

Conflict of interest: NR

Composition of ORS	H-ORS	Standard ORS recommended by WHO/UNICEF
Sodium, mmol/l	60	90
Potassium, mmol/l	20	20
Chloride, mmol/l	50	80
Glucose, mmol/l	84	111
Citrate, mmol/l	10	10
Made by dissolving the following in one litre of water		
NaCl, g	1.75	3.5
KCl, g	1.5	1.5
Trisodium citrate dehydrate, g	2.9	2.9
Glucose, g	15	20
Resulting osmolarity	224	311
Ten 1-litre packets were provided for each child		

N/A, not applicable; NR, not reported; ORT, oral rehydration therapy.

a Duration of diarrhoea does not fit with the inclusion criterion of acute diarrhoea for ≤ 72 hours.

b At discharge or on day 5 if they did not recover during this period.

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

Amadi *et al.* 2005[52]

Data extraction table

Reference and design	Intervention	Participants	Outcome measures
Author: Amadi *et al.*[52] and Amadi 2002[58] *Year:* 2005 *Country:* Zambia *Study design:* single-blind RCT *Setting:* inpatient [malnutrition ward in university teaching hospital (UTH)] *Number of centres:* one *Funding:* grant received from SHS International Ltd (Scientific Hospital Supplies); one author is supported by the Wellcome Trust	*Intervention:* Neocate amino acid-based elemental infant formula feed that excluded cow milk, soy and cereal antigens, 4 weeks (see end of table for details) *Control:* standard nutritional rehabilitation therapy for persistent diarrhoea and malnutrition using a skimmed milk/soy-based diet, 4 weeks (see end of table for details) *Other interventions used:* The UTH followed the WHO guidelines for management of persistent diarrhoea and malnutrition. All children received ORT with i.v. fluids given only when strictly indicated. All received oral micronutrient supplements and broad-spectrum antibiotics according to clinical condition Some children treated for TB on clinical grounds, usually after failure to respond to antibiotic therapy for pneumonia Children were tested for HIV infection and given full pre- and post-test counselling where indicated	*Definition of SAM:* used Wellcome classification to define malnutrition. States children had SAM and baseline WAZs were –4 *Number of participants:* $n=200$ (Neocate $n=100$, control: $n=100$) *Sample attrition/dropout:* 45/200 (22.5%): $n=24$ (12%) Neocate (22 died, two withdrawn); $n=21$ (10.5%) control (17 died, four withdrawn) Overall, 39 died and of the six withdrawn, three were discharged prematurely owing to a cholera outbreak (NR by group) and three withdrew (mothers needed at home) *Sample crossovers:* none *Inclusion criteria:* children aged 6–24 months with malnutrition and persistent diarrhoea (≥ 14 days duration) *Exclusion criteria:* children with features of measles, chickenpox, neurological disorder (e.g. cerebral palsy), serious systemic disorder or being exclusively breastfed *General characteristics of participants:* children with persistent diarrhoea and malnutrition, aged 6–24 months, 54% HIV+ve	*Primary outcomes:* ■ weight gain ■ diarrhoea ■ mortality *Secondary outcomes:* ■ developmental milestones achieved ■ activity and play ■ laboratory indicators of severity of illness (haemoglobin and albumin) *Method of assessing outcomes:* all feeds, fluid balance and stools passed were documented daily Weight recorded three times per week Lactose intolerance tested using Clinitest (Bayer Corporation, Pittsburgh, PA, USA). Blood sugar monitored during feeds and treated appropriately. All initial investigations repeated at the end of 4 weeks (except chest radiography and HIV testing) *Adverse symptoms:* none reported *Length of follow-up:* 4 weeks *Recruitment dates:* April 1998 to June 2000

Characteristics of participants

Characteristic	Neocate ($n=100$)	Control ($n=100$)	*p*-value
Sex, M:F	49:51	45:55	0.64
Age, months	17 (14–20)	18 (13–22)	0.31
Diagnosis:			
Underweight	10	9	
Marasmus	21	24	
Kwashiorkor	44	49	
Marasmic kwash	25	18	0.65
HIV infected[a]	51	54	0.86
Fever	24	34	0.15
TB			
Definite	13	14	0.98
Probable	15	21	0.35
Chest radiograph			
Normal	16	12	
Abnormal	69	83	0.35

Intestinal infection			
C. parvum	28	23	0.54
Salmonella sps.	23[b]	13	0.10
Giardia intestinalis	6	5	0.99
Shigella spp.	2	2	0.69
Ascaris	3	7	NR
Hookworm	1	2	NR
WAZ	–4.0 (–4.6 to –3.4)	–4.1 (–4.8 to –3.6)	0.38
HAZ	–2.9 (–3.6 to –2.1)	–3.0 (–3.6 to –2.1)	0.40
MUAC, cm	11 (10–12.2)	11 (10–12)	0.55
Haemoglobin concentration, g/dl	9.3 (8.3–10.1)	9.0 (8.3–10.0)	0.28
Serum albumin concentration, g/dl	28 (23–31)	29 (24–34)	0.41

Comments: results with brackets are median (IQR)

Text states 106 participants were HIV+ve, although tables suggests 105 participants

Results

Primary outcomes	**Neocate**	**Control**	***p*-value**
Weight gain, kg	*n* = 79	*n* = 78	
From admission	1.10 (0.55–1.55)	0.75 (0.2–1.3)	0.006
From nadir	1.7 (1.2–2.0)	1.2 (0.6–1.7)	0.002
Increase in WAZ	*n* = 79	*n* = 78	
From admission	0.83 (0.35–1.22)	0.43 (0–0.9)	0.018
From nadir	1.23 (0.89–1.57)	0.87 (0.47–1.25)	0.002
Increase in WHZ	*n* = 79	*n* = 78	
From admission	1.28 (0.52–1.88)	0.56 (0–1.15)	< 0.001
From nadir	1.77 (1.30–2.26)[c]	1.23 (0.59–1.70)	< 0.001
Increase in *z*-score from nadir in HIV+ve children	*n* = 38	*n* = 40	
W/A	1.2 (0.8–1.5)	0.70 (0.4–1.2)	0.007
W/H	1.8 (1.1–2.3)	0.8 (0.4–1.6)	< 0.001
Increase in *z*-score from nadir in HIV–ve children	*n* = 41	*n* = 38	
W/A	1.29 (0.98–1.57)	0.95 (0.5–1.45)	0.01
W/H	1.82 (1.47–2.38)	1.43 (0.81–1.86)	0.009
Mortality (over 4 weeks)	22% (22/100)	17% (17/100)	0.48
Mortality by nutritional status, *n* (%)			
Underweight	2 (10.5)		
Marasmus	12 (26.7)		
Kwashiorkor	10 (10.8)		
Marasmic kwashiorkor	15 (34.9)		0.004

Comments: data are presented as median (IQR)

Neocate was associated with a 41% better gain in weight

Diarrhoea, assessed as total number of stools passed over each time period, was not different in the two groups over the 28-days follow-up, nor was there any difference in stool frequency between the groups in the fourth week of follow-up (numerical data not presented in paper)

Similar numbers in each group were tested for malabsorption of reducing sugars and there was no significant difference in positive tests between the groups (numerical data presented, but not extracted)

Overall deaths = 19.5% (39/200), of which 31% was in week 1, 43% in week 2, 26% in week 3 and 10% in week 4. Amadi *et al.*[52] reports that death was more likely in children with marasmus, and children with cryptosporidiosis (data NR). However, Amadi[58] reports data and shows death was more likely in marasmic kwashiorkor

Mortality was lower in HIV–ve children than in HIV+ve children (11% vs 24%, respectively), irrespective of nutritional regimen

There was significant correlation between mortality and severity of initial diagnosis of nutritional status, and being HIV+ve, but these results were only reported for the overall study group, not by trial arm

Secondary outcomes – achievements of developmental milestones, activity and play and laboratory indicators of severity of illness (haemoglobin and albumin concentrations) – were reported, but have not been extracted here

Other outcomes	Neocate ($n=100$)	Control ($n=100$)	p-value
Week 1 Intake, kcal/kg/day	116 (86–143), $n=95$	167 (130–214), $n=97$	<0.0001
Week 2 Intake, kcal/kg/day	168 (135–203), $n=85$	258 (210–301), $n=93$	<0.0001
Week 3 Intake, kcal/kg/day	184 (166–206), $n=75$	283 (229–337), $n=85$	<0.0001
Week 4 Intake, kcal/kg/day	187 (163–210), $n=70$	269 (214–305), $n=79$	<0.0001

Comments: presentation of data believed to be median (IQR), but this is not explicitly state

Intake of calories (per kg per day), as liquid feeds for each of the 4 weeks of the study in the control group, were statistically significantly higher ($p<0.0001$). Note, in addition to the liquid feed (based on skimmed milk) intake in the control group, soy-based porridge was also given, beginning in week 2

Safety: NR

HIV: the Neocate diet benefit was seen in both HIV+ve and HIV–ve patients

The statistically significant improvement in weight gain was not only true for the Neocate group as a whole, but also for HIV+ve ($p=0.007$) and HIV–ve ($p=0.01$) children

Death was statistically significantly more likely ($p=0.04$) in HIV+ve children (23.6%, $n=25$) vs HIV–ve children (11.1%, $n=10$)

Barriers to implementation

Study authors did not believe an elemental feed such as Neocate should be adopted because of the expense. Fifty-one per cent (284/548) of eligible children were not randomised because no bed was available on the day when judged to be eligible. Rate of recruitment had to be limited as the number of eligible patients exceeded the capacity of the nursing staff and laboratory technicians to carry out the full range of study procedures and investigations. A cholera outbreak also temporarily interrupted the study leading to premature discharge of three patients

Methodological comments

Allocation to treatment groups: randomisation using consecutive sealed envelopes. The randomisation code was blocked so as to equalise active and placebo for every 20 patients

Blinding: single-blind (patients) study because of preparation and administration of feeds; apart from feeds, care was identical in all other respects. Study was double blind up until randomisation and single blind thereafter (care providers and outcome assessors not blinded). However, control group children were given porridge from week 2, thus, participants may have been aware, although knowledge of group assignment was not likely to affect outcomes as these were objective measures

Comparability of treatment groups: paper states that groups were well-matched; groups were not significantly different (p-values reported)

Method of data analysis: not ITT analysis. Comparison of categorical variables used chi-squared or Fisher's exact tests, and of continuous variables used the Kruskal–Wallis test

Sample size/power calculation: NR

Attrition/dropout: numbers and reasons reported. 45/200 (22.5%): $n=24$ (12%) Neocate; $n=21$ (10.5%) control. Of the 45 participants, 39 died ($n=22$, Neocate; $n=17$, control), three withdrew and three discharged prematurely because of cholera outbreak ($n=2$, Neocate; $n=4$, control)

General comments

Generalisability: likely that most of the children would meet the current WHO criteria of MUAC < 115 mm. Population was a subsection of children with SAM admitted to the unit (not all eligible children owing to limitation on resources), young infants (aged 6–24 months), approximately half were HIV+ve. Participants had a high prevalence of intestinal infection, respiratory and systemic infectious disease. The study was designed to investigate a feed for treatment of SAM in children with persistent diarrhoea, it is not clear whether or not this feed would be a suitable treatment for children with SAM, but who do not have persistent diarrhoea. None of those enrolled in the study were > 2 years of age so it is not clear whether or not the results of the study would hold in children aged ≥ 2 years

Outcome measures: outcomes appropriate although no numerical data for diarrhoea reported

Intercentre variability: N/A

Conflict of interest: a grant was received from SHS International Ltd (Scientific Hospital Supplies); the corresponding author is supported by the Wellcome Trust

Neocate infant formula feed	Standard nutritional rehabilitation therapy
Amino acid-based elemental feed (Neocate) + routine care	Standard therapy as per hospital protocol + routine care
Complete infant formula feed based on amino acids, maltodextrin and a combination of safflower oil, refined coconut oil and soya oil, with a calorific value of 70 kcal/100 ml. The vitamin and mineral composition reflects that of breastmilk	Complete feed: mixture of skimmed milk, sugar and vegetable oil given as a liquid feed (100 kcal/100 ml). At beginning of week 2, children given a soya-based, high-energy protein supplement in porridge form providing 400 kcal/100 ml, beginning at 100 ml/day and increasing to 200–300 ml/day

Liquid feeds given at 3-hour intervals (2 hours for weaker children) using cup and spoon or via nasogastric tube if necessary. Feeds were introduced gradually, beginning at 80 kcal/kg/day to avoid the refeeding syndrome. If diarrhoea worsened or reappeared, stools were tested for presence of reducing substances to detect lactose intolerance

If lactose intolerance test was positive (≥ 1%), feeds were diluted to half strength and gradually reintroduced to full strength	If lactose intolerance test was positive (≥ 1%), skimmed milk was withdrawn and replaced by a commercial fermented milk
Components of the WHO guidelines for management of persistent diarrhoea employed at UTH:	
Emphasis on oral/NG rehydration	If i.v. fluids are necessary (for severe dehydration and shock), they are given for shorter periods of 4–6 hours, with close monitoring and a change to the oral route as soon as improvement is noted
Vitamin, zinc, copper	Vitamins and mineral supplements given when available
Multivitamin	
Folic acid	
Potassium	
Antibiotics	Often necessary because these children have severe infections (e.g. septicaemia, pneumonia)
Antimalarials	Given because malaria is endemic in Zambia

HAZ, weight-for-age *z*-score; N/A, not applicable; NG, nasogastric; NR, not reported; ORT, oral rehydration therapy; WAZ, weight-for-age *z*-score; WHZ, weight-for-height *z*-score.

a HIV test results available for 196 children.

b Amadi[58] reports $n = 22$.

c Interquartile range given in paper (130–2.26), but we assume the 130 is an error and the value should be 1.30.

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 available.

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

Bhutta *et al.* 1994[53]

Data extraction table

Reference and design	Intervention	Participants	Outcome measures
Author: Bhutta *et al.*[53] *Year:* 1994 *Country:* Pakistan *Study design:* RCT *Setting:* inpatient (Gastroenterology-Nutrition Research Ward at the Aga Khan University Hospital, Karachi, Pakistan) *Number of centres:* one *Funding:* provided by the Applied Diarrhoeal Disease Research Project at Harvard University via a co-operative agreement with the US Agency for International Development	*Intervention (soy group):* soy formulation (full strength) *Control (KY milk group):* half-strength buffalo milk with KY Details of diet composition provided at end of table Both diets were provided for 14 days and given in gradually increasing amounts. Day 1 at least 50 kcal/kg/day, increasing by 25 kcal/kg/day to provide a minimum of 100 kcal/kg/day by day 3. Diets were given by nasogastric tube if children were unable to take the stipulated amount orally *Other interventions used:* NR	*Definition of SAM:* W/A ≤ 80th centile of the median NCHS standard, i.e. Gómez grades II and III malnutrition *Number of participants:* 51 (soy group, $n = 25$; KY milk group, $n = 26$) *Sample attrition/dropout:* after randomisation, 11 participants were subsequently excluded (four from the soy group and seven from the KY milk group); one for pneumonia, four for development of septicaemia, four for hyperpyrexia ≥ 39 °C, or withdrawal by the parents prior to completion of study protocol (two, one in each group) *Sample crossovers:* NR *Inclusion criteria:* male children, aged 6–36 months, with persistent diarrhoea (diarrhoea lasting ≥ 2 weeks), and with severe PEM *Exclusion criteria:* breastfed infants, presence of intercurrent infections, ileus and bloody diarrhoea. Children with kwashiorkor (clinical oedema and/or serum albumin ≤ 20 g/l) excluded because weight gain difficult to interpret in these children In addition, children admitted for the duration of the study were examined twice daily and excluded from the study if they developed a significant intercurrent illness (pneumonia, pyrexia ≥ 39 °C, persistent vomiting, or clinical signs of septicaemia) *General characteristics of participants:* economically disadvantaged children in Karachi (mean *z*-score W/A –4.2, SD 0.8)	*Primary outcomes:* stool output and weight gain (not explicitly stated, but assumed primary outcomes as used for sample size calculation) *Secondary outcomes:* not explicitly stated *Method of assessing outcomes:* vital signs, food and fluid intake, and stool, urine and emesis output were accurately recorded. Adhesive urine bags were used to collect urine separately from stools. Stool volume was measured by weighing pre-weighed diapers on electronic scales accurate to ± 2g (Tanita Inc., Amsterdam, the Netherlands). Daily nude weight obtained prior to morning feed on a double-beam balance accurate to ± 20 g (Detecto, Webb City, MO, USA). Length measured on an infant stadiometer, mid-arm circumference measured using fibreglass tape Growth quotient comparing actual daily weight gain with expected weight gain for age calculated using the method of Ellerstein and Ostrov[93] Clinical failure defined as weight loss for ≥ 3 days after meeting the minimum caloric target of 100 kcal/kg/day or persistence of diarrhoea with inability to maintain hydration orally Cessation of diarrhoea defined as passage of semisolid stool, a reduction of stool frequency to ≤ 3/day or a stool volume < 30 g/kg/day A range of laboratory investigations were carried out on stools daily, and metabolic balance studies on days 4–6 and 12–14 of dietary therapy on every third patient admitted (details not data extracted) *Adverse symptoms:* NR *Length of follow-up:* not explicitly stated, presumed to be 14 days *Recruitment dates:* NR

Characteristics of participants

Characteristic, all (mean ± SD)	Soy group (*n* = 25)	KY milk group (*n* = 26)	*p*-value
Age, months	16.0 ± 8.6	13.8 ± 5.8	NS
Weight, kg	5.8 ± 1.1	6.1 ± 1.1	NS
W/L (%)	88.4 ± 4.3	89.5 ± 4.3	NS
L/A (%)	71.1 ± 7.6	74.5 ± 9.1	NS
z-score W/A	–4.41 ± 0.6	–3.91 ± 0.9	NS
Mid-arm circumference, cm	9.9 ± 1.3	10.6 ± 1.7	NS
Total protein, g/dl	5.6 ± 0.9	6.1 ± 0.9	NS
Albumin, g/dl	3.4 ± 0.7	3.8 ± 0.7	NS
Haemoglobin, g/dl	9.5 ± 1.3	8.7 ± 1.4	NS
History			
Duration of diarrhoea, days	75.0 ± 77.0	150.0 ± 117.0	NS
Stool frequency, *n*/day	8.2 ± 2.7	8.1 ± 2.7	NS
Observations in first 24 hours			
Stool volume, g/kg/day	69.8 ± 51.9	62.3 ± 42.1	NS
Stool frequency, *n*/day	7.4 ± 4.7	7.1 ± 4.5	NS
ORS intake, ml/kg/day	47.0 ± 84.5	52.8 ± 77.3	NS
Urine volume, ml/kg/day	38.4 ± 21.3	30.0 ± 20.8	NS

Comments: median (range) duration of diarrhoea in the soy group was 180 (15–300) days and in the KY milk group 150 (15–270) days. Two patients in the soy group had pathogens in their stools (one entropathogenic *E. coli,* one *S. paratyphi a*), and one patient in the KY milk group had a parasitic infection (*G. lamblia*). Further information from laboratory investigation of stool samples not data extracted

Results

Primary outcomes	Soy group (*n* = 21)	KY milk group (*n* = 19)	*p*-value
Stool volume, g/kg/day			
Week one	68.8 ± 43.1	60.9 ± 40.6	NS
Week two	36.2 ± 23.2	63.9 ± 61.8	NS
Overall	58 ± 33	62 ± 49	NS
Weight change, g/kg/day			
Week one	7.1 ± 11.3	3.1 ± 12.1	NS
Week two	11.6 ± 10.0	4.3 ± 7.2	< 0.02
Mean daily weight change, g/kg/day	3.7 ± 5.9	7.9 ± 9.7	NS

Comments: not explicitly stated but presume data are mean ± SD

In the soy group, 10% (2/21) lost weight, in the KY milk group 37% (7/19) lost weight (*p* = NS)

Secondary outcomes	Soy group (*n* = 21)	KY milk group (*n* = 19)	*p*-value
Caloric intake, kcal/kg/day			
Week one	140.1 ± 33.4	115.1 ± 25.1	< 0.02
Week two	157.1 ± 72.3	151.6 ± 32.3	NS
Overall	154.2 ± 36.8	132.8 ± 27.6	NS
Stool frequency, *n*/day:			
Week one	7.0 ± 3.1	6.6 ± 4.4	NS
Week two	4.0 ± 2.4	5.5 ± 3.8	NS
Overall	6 ± 3	6 ± 4	NS
ORS intake, ml/kg/day:			
Week one	33.9 ± 41.0	37.9 ± 46.2	NS
Week two	1.7 ± 3.6	29.2 ± 58.1	< 0.05
Time to recovery	6 ± 4	5 ± 3	NS
Growth quotient over 14 days	13.6 ± 13.2	7.5 ± 6.9	NS
Improvement in MUAC, cm	1.0 ± 0.1	0.1 ± 0.05	< 0.001
Clinical failures	2	7	NR

Comments: not explicitly stated, but presume data are mean ± SD

Overall the soy group consumed nearly 15% more calories than the KY milk group, but the difference was NS. Only two children in each group required nasogastric feeding. The improvement in WAZ was significantly greater in the soy group (*z*-score from –4.4 ± 0.6 to –3.6 ± 0.6; $p < 0.001$) than in the KY milk group (*z*-score from –3.9 ± 0.9 to –3.6 ± 1.0; p = NS). Daily urine output and serum sodium levels after 48 hours of therapy were described as similar between the groups, but no numerical data presented

Data on normalisation of serum bicarbonate for a subgroup of children not data extracted

Data from two nutritional balance studies performed on a subgroup of children not data extracted. Details on the clinical failures not data extracted

Safety: NR

HIV: NR

Barriers to implementation

NR

Methodological comments

Allocation to treatment groups: block randomisation process using sealed envelopes

Blinding: not described, presume that study was not blinded

Comparability of treatment groups: described as similar with regard to age, degree of malnutrition and severity of diarrhoea prior to presentation. Stool volume, frequency, ORS intake and serum electrolytes in both groups were also described as comparable in the first 24 hours after the initiation of dietary therapy

Method of data analysis: data were analysed for differences between means using a two-tailed Student's *t*-test. Differences in proportions were assessed by chi-squared analysis

Sample size/power calculation: estimated that using an alpha-level of 0.05 and a power of 80%, 40 children in each group would be needed to demonstrate a 25% difference in stool output or weight gain between the study groups. However, the mid-term evaluation of the study identified more failures and significantly poorer weight gain the children receiving the KY and buffalo milk diet, and the study was therefore concluded with a total of 51 children randomised (and 11 of these were subsequently excluded)

Attrition/dropout: overall number excluded from the study after randomisation given, and deducible for each group from results tables. Reasons given for the population overall, but not by study group (except in stating that one from each group was withdrawn from the study by the parents prior to completion of the study protocol)

General comments

Generalisability: children initially identified as potentially eligible from the outpatient and emergency services of a large Government hospital in Karachi. Only male children enrolled (to allow for collection of urine and faeces separately), but it is likely that the results would be generalisable to girls. To be eligible children had to be ≤ 3 years, therefore, the results may not be generalisable to children aged 4–5 years old. The study ward had a research nurse and medical officer in constant attendance, this level of supervision may not be possible in all settings

Outcome measures: primary outcomes were not explicitly identified. Methods for assessing outcomes were reported, and definitions for outcome measures such as treatment failure were provided

Intercentre variability: not applicable

Conflict of interest: NR

Composition of buffalo milk + KY diet compared with the soy formula diet (based on feeding a 10 kg child at 120 kcal/kg/day)

	KY milk				
	Khitchri	Yoghurt	Buffalo milk (half strength)	Total	Soy formula
Volume, ml	376	260	1025	1661	1790
Calories, kcal	444	156	600	1200	1200
Carbohydrate, g	71.4	10.4	25.6	107.4	118.2
Protein, g	12.4	8.1	22.6	43.1	35.8
Fat, g	11.7	10.4	45.1	67.2	64.5
Other details	Mixed amounts of khitchri and yoghurt were provided at a 3:1 ratio and approximately 50–60% of the daily caloric intake was provided by buffalo milk Khitchri (60 g rice, 30 g lentils, 10 g dry weight cottonseed oil and 1 g salt) prepared in bulk by cooking lentils in water with rice and oil added subsequently until a homogeneous consistency achieved. Aliquots frozen and distributed under supervision of a clinical nutritionist Yoghurt and buffalo milk obtained regularly from a single commercial source. Lactose content of yoghurt 3.0 g/dl, and of half-strength buffalo milk 2.5 g/dl				One hundred grams of powder consisted of soy protein (15.5 g), glucose polymers (50 g), a fat blend (28 g) of equal amounts of corn oil and coconut oil, and the recommended dietary allowance of vitamins and minerals. Also fortified with L-methionine, taurine, and L-carnitine, and had an osmolality of 200 mOsm/kg

L/A, length-for-age; NR, not reported; NS, not statistically significant.

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; WAZ, weight-for-age *z*-score.

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

Nurko *et al.* 1997[56]

Data extraction table

Reference and design	Intervention	Participants	Outcome measures
Author: Nurko *et al.*[56] *Year:* 1997 *Country:* Mexico *Study design:* double-blind RCT *Setting:* inpatient (Hospital Infantil de Mexico Federico Gómez, Mexico City) *Number of centres:* one *Funding:* part-funded by Applied Diarrhoeal Disease Research Project at Harvard University, by means of a co-operative agreement with the US Agency for International Development and in part by a National Institutes of Health grant (T32-DK 07703)	*Intervention 1:* local chicken-based diet *Intervention 2:* soy diet – Nursoy (Wyeth Laboratories) *Control:* elemental diet – Vivonex Standard (Norwich Eaton) See end of table for details Diets differed in macronutrient composition and started at the lowest concentration (150 ml/kg/day) via a nasogastric tube and concentrations were advanced every 48 hours after initial overnight fast and hydration. Full concentration was achieved by the ninth day if no intolerance occurred, otherwise the concentration was either: maintained if there were 2% or 3% positive reducing substances (before or after hydrolysis) or if there was an increase in stool output of >50% (>20 ml/kg); or decreased if Clinitest results showed 4% or there was an increase of ≥75% in stool output (>20 ml/kg). Cases received 7 days of the maximum diet concentration, followed by whole cows milk administered half-strength (10 ml/kg) and advanced to full strength if tolerated. Milk-tolerant cases continued with lactose-containing formula or whole milk, depending on age (no further details reported). If lactose-intolerant (i.e. return of liquid stools with pH <5 and >2% reducing substances in the stool, a milk-free diet was instituted *Other interventions used:* cases were hydrated on admission following WHO/UNICEF guidelines (standard glucose-electrolyte i.v. solution). When the maximum concentration of the diet was achieved, daily supplementation with 1 mg folic acid, 1 ml multivitamin (Poly-Vi-Sol), and 6 mg/kg elemental iron was added. Suspected systemic infections were treated with broad-spectrum i.v.-administered antibiotics. Otitis media, urinary tract infections and pneumonia were treated with appropriate antibiotics, and dysentery with trimethoprim–sulfamethoxazole and children infected with *G. lamblia* with metronidazole	*Definition of SAM:* third-degree malnutrition of the marasmatic type as defined by the Gómez criteria. W/A <60% of the NCHS 50th percentile *Number of participants:* *n*=56 (enrolled, *n*=60; chicken, *n*=19; Nursoy, *n*=19; Vivonex, *n*=18) *Sample attrition/dropout:* *n*=15 (27%) treatment failures (Chicken, *n*=4; Nursoy, *n*=6; Vivonex, *n*=5). Of these five died (Chicken, *n*=2; Nursoy, *n*=1; Vivonex, *n*=2) and 10 successfully managed and discharged home *Sample crossovers:* none, although 15 treatment failures (see *Sample attrition/dropout*) changed diets (chicken and Nursoy for Vivonex; parental nutrition then enteral Vivonex for those originally on Vivonex diet). However, these children discharged home and were not counted as crossovers per se *Inclusion criteria:* children aged 3–36 months with third-degree malnutrition of the marasmatic type and persistent diarrhoea (defined as three or more loose stools for ≥14 days) *Exclusion criteria:* ■ Exclusively breastfed ■ Chronic illness (i.e. AIDS, TB) ■ Congenital malformation ■ An abdominal condition that would preclude enteral feedings a severe condition requiring intensive care ■ Lack of parental consent *General characteristics of participants:* children aged 3–36 months with SAM and PD *Associated conditions on admission:* 64% (non-gastrointestinal infection 50%, gastrointestinal infection 14.3%)	*Primary outcomes:* not specifically reported *Outcomes:* diarrhoea status, weight, nitrogen balance, nutritional recovery, treatment success and failure *Method of assessing outcomes:* all measurements were obtained by trained nutritionists and their accuracy was validated before start of study. All intake/output was recorded, nasogastric tube was inserted by trained nursing staff ■ Nude weight – electronic scale (Tronix, Wheaton Ill, Wheaton, IL, USA) accurate to at least 10 g on admission, the morning of the start of the diet (i.e. post-hydration weight was baseline weight) and same time every morning thereafter ■ Recumbent length (measured using specially designed board, no further details) on admission, at the end of 2 weeks and before discharge ■ Baseline laboratory values at admission, including complete blood cell count, electrolyte concentrations, D-xylose concentration, stool and urine cultures, and stool tests for ova and parasites ■ Blood culture specimens were obtained only if indicated ■ Nitrogen: 72-hour, balance test at end of second week (starting 4 days after the maximum diet concentration achieved). Nitrogen balance measured by the micro-Kjeldahl method. Tests for pH and reducing/non-reducing substances in stool were performed daily (no further details) ■ Stool collection: beginning and end of the time were marked by the faecal excretion of orally administered activated charcoal. All children were placed on metabolic beds/cots for separation of stool from urine. To confirm successful separation of stool and urine for girls, a separate analysis for all the variables associated with stool collection was performed at end of study *Definitions:* ■ Cessation of diarrhoea: passage of formed stool not followed by liquid stools for ≥24 hours ■ Successful treatment: able to advance formula to highest concentration and cessation of diarrhoea at end of the study

- Onset of nutritional recovery: diarrhoea ceased and consistent weight gain for ≥ 48 hours
- Treatment failure: ≥ 5% dehydration during administration of diet clinical deterioration precluding further enteral therapy diarrhoea persisting until end of study, or if unable to advance formula to full concentration[a]

Adverse symptoms: diet intolerance and intestinal pneumatosis

Length of follow-up: NR, approximately 9 days if no intolerance to diet + addition 7 days

Recruitment dates: NR

Characteristics of participants

Characteristic	Chicken (*n* = 19)	Nursoy (*n* = 19)	Vivonex (*n* = 18)	Total (*n* = 56)
Age, months (SD)	6.7 (3.7)	5.6 (4.0)	6.9 (5.3)	6.4 (4.4)
Sex, *n* (M : F)	10 : 9	11 : 8	9 : 9	30 : 26
Initial weight, g (SD)	3647.3 (884.4)	3575.3 (1397.1)	3589.8 (1393.5)	3604.1 (1232)
Per cent W/A (% NCHS) (SD)	50.8 (7.4)	51.0 (7.5)	52.9 (7.5)	51.4 (7.2)
Weight *z*-score (SD)	–4.2 (1.0)	–3.9 (0.7)	–4.0 (1.2)	–4.0 (1.0)
Diarrhoea duration, days (SD)	36.6 (3.9)	48.7 (5.1)	41.8 (4.0)	42.4 (4.4)
Severe dehydration, *n* (%)	4 (21.1)	5 (26.3)	6 (33.3)	15 (26.8)
Faecal output, ml/kg/day (SD) – first 24 hours	41.6 (12.1)	45.8 (13.6)	52.3 (19.6)	46.4 (15.1)
Laboratory tests, (SD)				
Sodium, mmol/l	135.3 (7.8)	138.3 (6.9)	137.6 (6.1)	137.1 (6.9)
Potassium, mmol/l	3.9 (0.8)	4.2 (1.0)	4.3 (0.9)	4.1 (0.9)
Bicarbonate, mEq/l	15.5 (3.4)	15.1 (3.8)	16.5 (5.3)	15.7 (4.2)
Blood urea nitrogen, mg/dl	22.0 (8.6)	24.8 (14.9)	29.2 (14.6)	24.9 (13.1)
Albumin, g/dl	3.0 (0.6)	3.3 (0.6)	3.2 (0.6)	3.2 (0.6)
D-xylose, mg/dl	22.1 (7.8)	19.0 (10.5)	25.6 (13.9)	22.2 (11.0)
Associated conditions on admission, *n* (%)				
None	6 (31.6)	9 (47.4)	5 (27.8)	20 (35.7)
Sepsis	5 (26.3)	7 (36.8)	5 (27.8)	17 (30.4)
Urinary tract infection	2 (10.5)	3 (15.8)	2 (11.1)	7 (12.5)
Pneumonia	2 (10.5)	0	2 (11.1)	4 (7.1)
+ stool culture	2 *Shigella* (10.5)	0	2 *Shigella*, 1 *Salmonella* (16.6)	5 (8.9)
+ stool ova and parasites	1 *G. lamblia* (5.2)	0	1 *Cryptosporidium* (5.5)	2 (3.6)
+ stool culture + ova and parasites	1 *Salmonella* and *Cryptosporidium* (5.2)	0	0	1 (1.7)

Comments: results are mean (± SD) unless otherwise stated

No significant differences between groups (*p*-values NR)

Results

Outcomes	Chicken ($n=15$)	Nursoy ($n=13$)	Vivonex ($n=13$)	p-value
Diarrhoea status, (SD)				
Mean total stool output/kg/day	19.1 (7.5)	18.5 (6.6)	18.8 (9.2)	NS
Mean stools/day (SD)	3.2 (1.2)	2.5 (0.7)	3.4 (1.3)	
Day of cessation (SD)	6.9 (4.7)	3.9 (3)	8 (5.1)	NS
Weight, g (SD)				
At admission	3572 (823)	3270 (1167)	3764 (1575)	
At end of protocol	3736 (870)[b]	3495 (1172)[b]	3940 (1599)[b]	
At time of discharge	4133 (1160)[c]	3797 (1128)[c]	4225 (1706)[c]	
Mean number of total calories/kg/day after full diet tolerated (SD)	116.0 (9.6)	111.3 (9.1)	115.2 (8.3)	NS
Protein/kg/day ingested after full diet tolerated, g (SD)	3.5 (0.4)	3.4 (0.3)	2.4 (0.2)	<0.05
Nitrogen balance, mg/kg /day (SD)	358.2 (13)[d]	291.4 (111.6)	226.6 (61.2)	
Per cent absorption	86.0 (10.8)	85.9 (8.5)	89.5 (5.4)	
Per cent retention	60.7 (19.3)	50.9 (16.8)	59.3 (14.0)	
Biological value	69.7 (17.3)	58.7 (16.8)	66.1 (14.4)	
Nutritional recovery, *n* (%)	13 (86.6)	12 (85)	10 (77)	
Successful outcome, *n* (%)	15 (78.9)	13 (68.4)	13 (72.2)	NS
Safety, *n* (%)[e]				
Some formula intolerance	9 (47.4)	11 (57.9)	14 (77.8)	NS
Treatment failure, *n*	4	6	5	
Mean time from diet start to failure, hours (SD)	97.5 (99.9)	98.5 (99.9)	60.6 (45.7)	NS
Intestinal pneumatosis, *n*	1	1	2	
Death, *n*	2	1	2	NS

Comments: Chicken group had a significantly higher nitrogen balance ($p<0.02$) and states tendency towards a higher number of nutritional recoveries (NS), but no *p*-value reported

Results per serum albumin and D-xylose concentration, electrolyte abnormalities and results for milk tolerance tests were also reported, but not data extracted

Treatment success all: $n=41$ (73.2%)

Formula intolerance all: $n=34/56$ (61%), of which transient formula intolerance $n=19/34$ (56%)

Treatment failure all: 15 (44%)

Mean time from diet start to failure all: 85.6 (72 hours); one treatment failure (Nursoy) was because of allergy to the formula, 10 treatment failures were successfully managed: *Mean stay (SD):* 50 (30) days

Death all: $n=5$ (8.9%) because of intestinal pneumatosis ($n=2$), central line-associated sepsis ($n=2$), bacterial sepsis (*K. pneumoniae*) ($n=1$)

Sodium concentration <130 mmol/l (RR 3.07, 95% CI 1.41 to 6.64) and presence of associated infections (RR 3.61, 95% CI 1.1 to 14.42), particularly *Crytosporidium* (RR 4.15, 95% CI 1.53 to 6.9), were associated with treatment failure

Significant differences ($p<0.05$) between treatment success and failure associated with albumin (3.2 vs 2.9 g/dl), sodium concentration (138.4 vs 133.5 mmol/l) and the incidence of associated infections (56.1 vs 86.7%). There were additional differences in stool output on the second day (20.9 vs 47.4 ml/kg) and third day (16.7 vs 54.0). Differences in serum albumin and D-xylose concentration, electrolyte abnormalities and results for milk tolerance tests were also reported, but not data extracted

Intestinal pneumatosis all: 7.14%

HIV: N/A

Barriers to implementation

None reported

Methodological comments

Allocation to treatment groups: cases randomly assigned to treatment using a table of random numbers

Blinding: only the nutritionist who prepared the formula was aware of assignment group. Investigators, nurses and residents remained masked to the type of diet. Aluminium foil was used to cover the formula bag and tubing. Code was broken for treatment failures and diet changed

Comparability of treatment groups: states no significant differences between groups (no *p*-values reported), but Nursoy group was slightly younger and had higher percentage of children without associated conditions or infections with parasites on admission

Method of data analysis: descriptive analyses were used to define the presenting characteristics. To test differences between the groups, multivariate and repeated-measures analyses of variance were used. The data were transformed if they were not normally distributed (no further details reported). Duration of the diarrhoea was compared using survival analysis and chi-squared tests used for categorical variables. For small cells, the Fisher's exact test was used (no definition of small cells was given). Statistical analysis were performed using SPSS/PC and Epi-Info software (version 5.01; Centers for Disease Control and Prevention, Atlanta, GA, USA), with significance assumed when $p < 0.05$

Sample size/power calculation: it was calculated that a sample size of 20 children per group would be needed assuming a power of 0.80, an alpha of 0.05 and a difference of 30% in the duration of diarrhoea (no further details reported). A separate analysis was performed to confirm successful separation of stool and urine in girls for all the variables associated with the stool collection at the end of the study. As no differences between sexes were found (data not shown), all data were pooled, however, the analysis is unlikely to be powered

Attrition/dropout: numbers and reasons per treatment group reported

General comments

Generalisability: SAM defined using the Gómez criteria of W/A < 60% of the NCHS's 50th percentile would appear to meet the WHO criteria for SAM. To be eligible children had to hospitalised in a children's hospital in Mexico, be aged 3–36 months with third-degree malnutrition of the marasmatic type and persistent diarrhoea. The results may not be generalisable to younger or older children

Outcome measures: appear to be suitable and appropriate. Primary outcomes were not explicitly identified, but methods for assessing outcomes were reported and definitions for outcome measures such as treatment failure were provided

Intercentre variability: N/A, one centre only

Conflict of interest: none reported

Composition of diets at maximum concentration	Chicken	Nursoy	Vivonex
Total calories, kcal/dl	85.6	82.0	84.87
Protein, g/dl	1.7	2.5	2.6
Carbohydrate, g/dl	19.5	8.3	10.7
Fat, g/dl	0.1	4.3	3.5
Sodium, mEq/dl[f]	1.7	1.3	1.6
Potassium, mEq/dl[g]	2.5	2.3	2.2
Calcium, mg/dl	47	72	47
Phosphorus, mg/dl	47	50	47
Magnesium, mg/dl	19	8	18
Zinc, mg/dl	0.78	0.65	0.11
Osmolarity, mOsm/l	420	292	292
Percentage of total calories			
Protein	7.94	12.1	12.2
Carbohydrate	90.9	40.4	50.5
Fat	1.12	47.1	37.2

Total calories/total protein per day[h]	128.4/2.6 Diet was designed with the use of food composition tables: 8 g boiled comminuted chicken breast; 3 ml vegetable cooking oil; 10.5 g table sugar. Components were blended and minerals added: 5 ml calcium gluconate (10% solution, PISA); 2.7 ml of dibasic sodium phosphate (PISA); 1.7 ml of magnesium sulphate (10% solution, PISA). Boiled water was added to achieve the total volume required (150 ml/kg per day)	123.0/3.8 Soy formula contained soy protein, coconut, safflower and soy oils, sucrose, minerals and vitamins	127.4/3.9 Vivonex contains crystalline amino acids, glucose and glucose oligosaccharides, a small amount of highly purified safflower oil, electrolytes, minerals, micronutrients and vitamins Starting at 150 ml/kal per day in a concentration that provides 47.8 kcal/dl (12.5% weight/volume) and advancing slowly by 2.5% per day to a maximum concentration of 85.6 kcal/dl (22.5% weight/volume)
After the milk challenge, all cases restarted a complete age-appropriate, complex-balanced diet, continued until discharge. All diets were prepared in the paediatric nutrition kitchen of the hospital under the supervision of a trained nutritionist			

AIDS, acquired immunodeficiency syndrome; N/A, not applicable; NR, not reported; NS, not statistically significant; PD, persistent diarrhoea.

a When cases were declared treatment failure, those on a Nursoy or chicken diet were started on Vivonex. For those on Vivonex or unable to continue with enteral feedings, total parenteral nutrition alone was initiated and continued until stabilisation and weight was achieved, followed by the addition of continuous enteral feedings with Vivonex (advanced every 24 hours as tolerated). Once full enteral feedings is achieved, Vivonex diet continued for another 2 weeks (nutritional rehabilitation continued as outlined above).

b $p < 0.05$ at admission vs at end.

c $p < 0.05$ at admission vs at discharge.

d $p < 0.05$ comparison between the three groups.

e The percentage relates to the study populations before dropouts (Vivonex, $n = 18$; Nursoy, $n = 19$; chicken, $n = 19$).

f Sodium chloride was added to achieve a sodium intake of 4 mEq/kg/day per person.

g Potassium was added to achieve a potassium intake of 3 mEq/kg/day per person.

h Given at 150 ml/kg/day (calories measured in cal/kg body weight/day; protein measured in grams of protein/kg body weight/day).

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		

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