Management of oedematous malnutrition in infants and children aged >6 months: a systematic review of the evidence

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Abbreviations

CI	confidence interval
CMAM	Community Management of Acute Malnutrition
F-75	therapeutic milk used in stabilization phase of the treatment of SAM
HIV	human immunodeficiency syndrome
IQR	interquartile range
MAM	moderate acute malnutrition
MUAC	mid-upper arm circumference
RCT	randomized controlled trial
RUTF	ready-to-use-therapeutic-food
SAM	severe acute malnutrition
SD	standard deviation
W/A	weight-for-age
W/H	weight-for-height
WHO	World Health Organization
WHZ	weight-for-height z-score

Measurements

d	day
cm	centimetre
g	gram
kcal	kilocalorie
kg	kilogram
mg	megajoule
mm	milimetre
n	number

Abstract

Background
Children presenting mild or moderate nutritional oedema are usually treated in outpatient care. However, it is still unclear whether such children presenting require special care and if they can be treated indifferently in inpatient or outpatient care.

Methods
We systematically searched Medline, Embase, the Cochrane Library and DARE for evidence on mortality, recovery, treatment duration, weight gain, cost-effectiveness and adverse events in children with nutritional oedema treated in outpatient care as compared to treatment in inpatient care or to treatment of marasmus in outpatient care. We complied with the PRISMA statement for reporting of systematic review.

Results
Eight studies met the inclusion criteria, among which six observational studies and two controlled trials. These two trials assessed outcomes of outpatient care after one week of inpatient stabilization, i.e. not direct outpatient care. The first trial in Malawi reported better results in outpatients than in inpatients (recovery: 72% vs 49%) probably related to more infections in inpatient care. The second trial in Bangladesh reported the reverse (recovery: 67% vs 86%) but no food supplement was provide to outpatients. The recovery rates for outpatients ranged across studies from 69% to 96%. These rates were consistently higher than for those children with marasmus (range 33–81%) or marasmic kwashiorkor (range 45–71%), and mortality rates were consistently lower. No evidence on cost-effectiveness or adverse events was available. Overall, the quality of the evidence was low.

Conclusion
Oedematous malnutrition could plausibly be treated effectively in outpatient service. However, the quality of evidence was low and further good quality studies in various settings are required before conclusive guidance can be generated.

Background and objective

Along with a low mid-upper arm circumference (MUAC <115 mm) or a low weight-for-height <-3 z-score (WHZ; WHO 2006 growth standards), bilateral pitting oedema, also called nutritional oedema, is an independent indicator of severe acute malnutrition (SAM) in 6–59 month old infants (*1*). Three grades of severity are distinguished: oedema + is defined as a mild oedema on both feet/ankles; oedema ++ is a moderate oedema on feet and lower legs, hands or lower arms; and oedema +++ is severe oedema generalized to feet, legs, hands, arms and face *(2,3)*.

The standard recommendation for the management of SAM has been inpatient care during the stabilization and rehabilitation phases (*4*). However, inpatient treatment is resource intensive and requires many skilled and motivated staff, which is often lacking in low- and middle-income countries where SAM is common (*3*). Moreover, studies have shown that children with SAM could be adequately treated at home *(5–8)*. These results have led to a revised classification that categorizes acute malnutrition in complicated cases, which require inpatient care in the first stage of treatment, and uncomplicated cases that can be treated in the outpatient setting or at the community level (*3,9*). In the absence of severe illness and if an adequate appetite is maintained, SAM is considered uncomplicated. Regarding nutritional oedema, only children with oedema +++ or oedema +/++ combined with either a low MUAC, poor appetite or a severe illness should be hospitalized in the first stage of the treatment (*3*). These recommendations apply in many countries. Among 33 national guidelines on Community Management of Acute Malnutrition (CMAM) collected by the Emergency Nutrition Network in November 2011 (http://cmamconference2011.org/latest-conference-updates/), almost all admitted uncomplicated oedema +/++ to outpatient care if there was good appetite (Annex 1). There were only six countries in which nutritional oedema, regardless of its severity, was systematically referred for inpatient treatment (Angola, Mali, Mozambique, Niger, Tanzania and Zanzibar) and another two where only oedema + was admitted to outpatient care (Côte Ivoire and Kenya).

A recent joint statement by the World Health Organization (WHO), the United Nations Children's Fund and the World Food Programme also advocates treating children with SAM at the community level whenever possible (*10*). However, this guidance does not differentiate grades of oedema and states generically that "children can be transferred from facility to community-based care when their oedema is reduced" (*10*). Actually, it is still unclear whether children presenting nutritional oedema +/++ require special care and if they can be treated indifferently in inpatient or outpatient care, i.e. if the critical outcomes of survival and recovery are similar in both settings. Until now, the evidence has not been reviewed in a systematic way.

We, therefore, aimed at summarizing the evidence on the effectiveness and safety of managing children >6 months with uncomplicated oedematous SAM grade +/++ in outpatient care. This assessment is done by comparison with results obtained in the in-patient treatment of similar cases or in the out-patient treatment of uncomplicated SAM children without oedema (low WHZ and/or low MUAC) (Table 1). The results of this review will inform future policies on a safe and effective management of oedematous malnutrition.

Table 1
Research question (SPICE criteria)

Setting	Low- and middle-income countries, primary health care
Perspective/**P**opulation	Children >6 months with oedematous SAM +/++, and good appetite or no medical complications

Intervention	Community-based therapeutic care – outpatient management
Comparison	- Uncomplicated nutritional oedema +/++ treated in inpatient care or health service-based care - SAM cases without oedema treated in outpatient care
Evaluation	(1) short-term mortality (2) recovery rate (3) time to recover (4) weight, length, and MUAC gain (5) use of resources, costs (6) adverse effects

2. Methodology

2.1 Sources and key words for literature review

We searched Medline via PubMed (http://www.ncbi.nlm.nih.gov), Embase (http://www.embase.com), the Cochrane Library (www.cochranelibrary.com) and DARE (http://www.crd.york.ac.uk). We also searched the Emergency Network website (http://ennonline.net/) for additional field reports, and screened the bibliography of included studies.

We applied the following search strategy:

#1. (((Nutrition Disorders[MeSH] OR Growth disorders[MeSH] OR malnutrition[MeSH] OR wast*) AND (oedema OR edema)) OR "Kwashiorkor"[Mesh])
#2. (child[Mesh] OR infant[Mesh])
#3. ((Child Nutrition Disorders[MeSH] OR Infant Nutrition Disorders[MeSH]) AND edema)
#4. (#1 AND #2) OR #3
#5. (treatment OR rehabilitation OR management OR hospitalization OR community health services)
#6. #4 AND #5
#7. (editorial [pt] OR letter [pt] OR comment [pt])
#8. #6 NOT #7

The search strategy was adapted to fit each individual database (Annex 2). We searched for studies published up to 08 July 2013. We contacted the authors whenever additional data or clarifications on the published studies were needed. All publications were integrated into Reference manager version 12 (ISI ResearchSoft, Thomson Reuters).

2.2 Criteria of inclusion and exclusion

We included all original studies combining the three following criteria: (i) observational or interventional studies reporting on the outpatient treatment of children >6 months with nutritional oedema. Studies including children with and without oedema were retained if the subpopulation with oedema represented ≥80% of the study population or if the results on children with oedema were reported separately; (ii) studies reporting on any of the following treatment outcomes: mortality; nutritional recovery; weight/length/MUAC gain; adverse effects; and cost or cost-effectiveness of treatment; and (iii) studies carried out in low- and middle-income countries, as defined by the World Bank. We excluded editorials, letters or comments; studies including only children older than 60 months of age; and studies in languages other than English, French and Spanish.

2.3 Review process

We first screened titles and abstracts of identified references based on the inclusion criteria. Papers for which the title and/or abstract indicated that inclusion criteria could be fulfilled were considered and read in full. Two researchers applied the selection process independently. In case of discrepancies, a third reviewer was consulted and the decision to include or exclude the paper was reached by consensus. Studies excluded at this second stage are reported, as well as the reason for their exclusion. Data from included studies were extracted in predefined standard tables by one reviewer (NH) and cross-checked by a second one (DR).

2.4 Quality appraisal

The quality appraisal for the selected studies was derived from the checklists of the Scottish Intercollegiate Guidelines Network (http://www.sign.ac.uk/methodology/checklists.html). We adjusted the existing checklist for cohort studies to fit case series, as this was the main design of included studies. The selected quality criteria were: (i) adequate sampling of subjects (i.e. study not performed on a very specific subpopulation with limited external validity); (ii) management of missing values (% incomplete data, % of loss-to-follow-up, potential effect of missing data on results assessed or discussed); (iii) quality of measurement (training of assessors described, double measurements of anthropometry parameters, quality control procedures, assessment of accuracy); and (iv) appropriate statistical analysis. Each item was rated independently by two reviewers as: adequately addressed; moderately addressed; poorly addressed; or not reported. Disagreement between reviewers was resolved by discussion until a consensus was reached. In cases of a disagreement, a third reviewer was consulted. We followed the PRISMA statement for good reporting of systematic reviews (http://www.prisma-statement.org/).

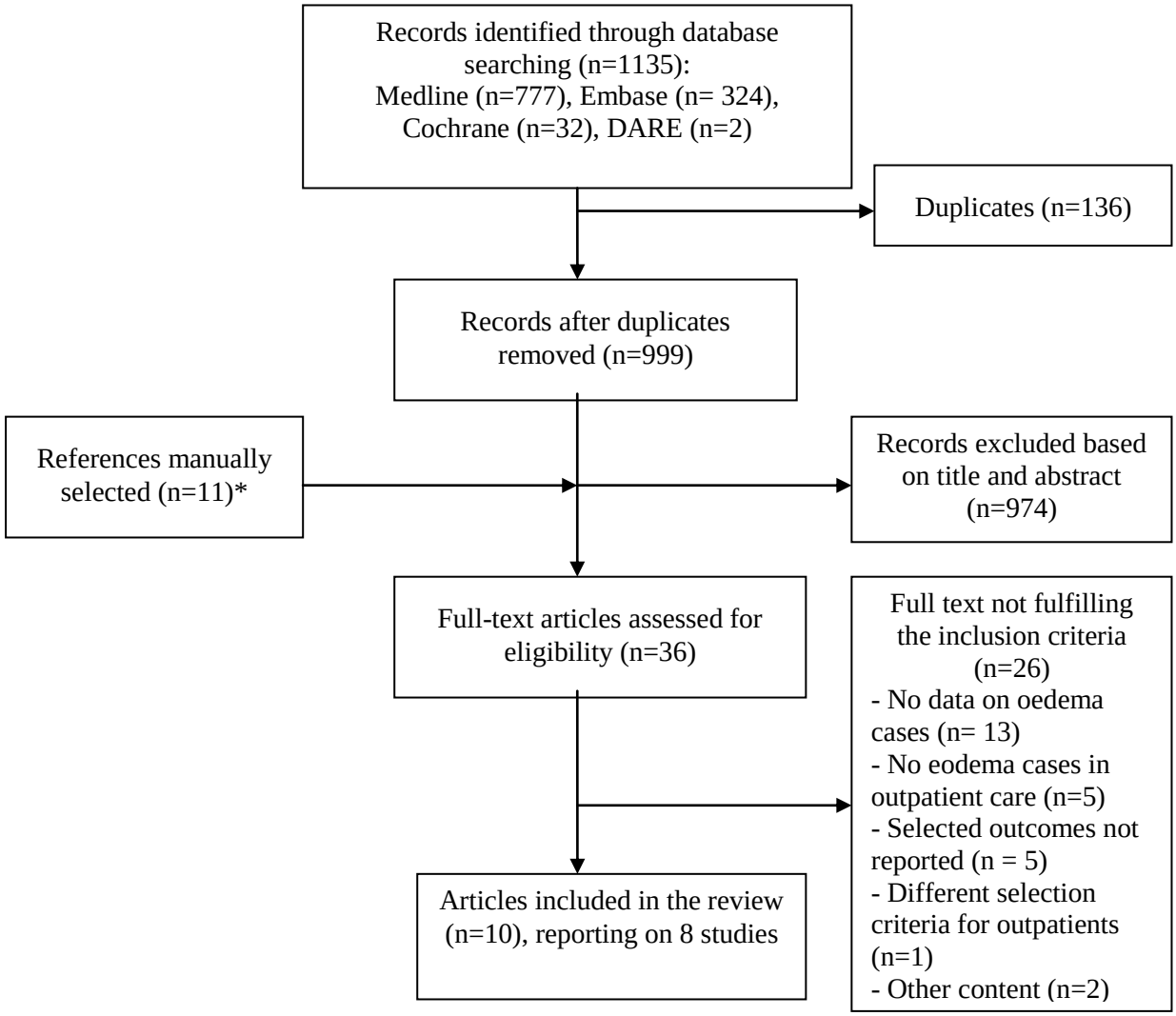
2.5 Appraisal of program performance

We compared the results reported in the studies with the international standards for good care of malnourished children (*11*). According to the Sphere guidelines, the main outcome indicators for success of management of severely malnourished children are mortality rates <10%, recovery rates >75%, a recovery time of 30–40 days, default rates <15% and weight gain > 8 g/kg/day. For fatality rate, we applied the method of Prudhon et al. to calculate the predicted case fatality rate and compare it to the actual case fatality rate as reported in the studies (*12*).

3. Results

We retrieved 999 references from the electronic databases of which 10 papers, reporting on 8 original studies, were included (Figure 1). Ashworth et al. 1997 (*13*) reported in more detail on the cost-effectiveness of the controlled trial published in 1994 by Khanum et al. (*14*). Ciliberto et al. 2006 (*6*) reported on children with oedematous malnutrition treated in outpatient care whose outcomes had already been presented with a 75% overlap in a previous publication (*15*) (personal communication of Mark Manary). Annex 3 gives an overview of excluded studies and reasons for exclusion.

Figure 1: Flow chart of review



* References found in the reference list of selected papers. None was retained for this review.

3.1 Characteristics of studies

None of the eight included studies was a randomized controlled trial (RCT) comparing the outcomes of children with uncomplicated oedema treated exclusively in outpatient vs inpatient setting (Table 2). Three controlled trials provided useful information, although their focus differed somewhat from our research question. An RCT with sequential allocation compared the outcomes of SAM children (98% with oedema) treated in inpatient, day care or home care after one week of day care in Bangladesh *(13,14)*. Another non-RCT compared the outcomes of children with SAM (81% oedema) who received inpatient vs home-based care for the second phase of treatment for childhood malnutrition (*6*). Finally, an RCT compared the outcomes of two types of ready-to-use-therapeutic-food (RUTF) during home-based care of children with SAM (78% with nutritional oedema) (*16*). Five observational studies

reported on the outcomes of oedematous malnutrition *(5,17–20)*, among which four treated children exclusively in an outpatient setting. Therefore, evidence on treatment of oedematous malnutrition treated in exclusive outpatient settings originated from five observational studies – although the study by Oakley et al. (*16*) was an RCT, it was observational in essence regarding the research question addressed in this review. Three additional studies provided evidence on the outcomes of oedematous malnutrition after one week of inpatient stabilization, two of which were RCTs aimed at comparing outcomes obtained with outpatient vs inpatient treatment (*14,15*).

The gradation +/++/+++ was not used in any of the included studies. In three studies, oedema was graded as severe according to the depth of imprint that remains when the thumb is removed from the foot dorsum: >0.5 cm *(6,15)* or >1.0 cm *(5,17)*. Children with severe oedema were excluded from these studies. No oedema gradation was defined in the remaining five studies. It is thus assumed that cases of severe oedema were included although the proportion was not reported *(3,14,16,18,20)*.

Five studies included a proportion of children who combined wasting and bilateral oedema, but reported results separately for marasmus, kwashiorkor or marasmic kwashiorkor treated as outpatients *(6,16,18–20)* (Table 5). Marasmic kwashiorkor was defined as the presence of bilateral pitting oedema and a WHZ <-3, except in one study in which wasted children were defined as having a WHZ <-2 (*6*).

The population of children ranged from 6–60 months, but two studies excluded children under 10–12 months *(6,14,15)* and another included children until 120 months (*3*). The eight studies recruited a total of 9616 severely malnourished children, from which the majority (81%) had oedema; 75% of oedema cases were treated solely in outpatient. Nearly all studies (7/8) took place in African countries and six of eight studies occurred in Malawi.

3.2 Outcomes of intervention

Tables 3–5 summarize the outcomes of the therapeutic nutritional interventions.

3.2.1 Recovery rate

The recovery rates for children with oedema treated in outpatient care ranged across studies from 69% to 96% (Table 3). These rates were consistently higher than for those children with marasmus (range 33–81%) or marasmic kwashiorkor (range 45–71%).

Two studies compared outcomes in children treated in outpatient care after one week of stabilization in inpatient setting vs full inpatient care (Table 4). In Malawi, the recovery rate of severely malnourished children (81% of whom presented oedema) managed in outpatient care during the second phase of treatment vs inpatient was, respectively, 72% and 49% at eight weeks (*15*). The proportion of children with oedema was equal in each group, but their specific recovery rates were not reported. However, the authors reported that in a subgroup of 171 children with oedema who were treated exclusively in outpatient management the recovery rate was 89% (*6*). Another study in Bangladesh compared the recovery rate of SAM children (98% of whom presented with oedema) in inpatient care vs day care vs home care after one week of day care and found, respectively, 87%, 67% and 75% (*14*). At the start of home care, 80% of children still had oedema and all recovered (personal communication of the author). No food supplements were distributed in this latter group.

3.2.2 Mortality rate

The mortality rates for children with nutritional oedema treated in outpatient care reported in six studies ranged from 1% to 4%, but peaked at 16% in a seventh study (18) (Table 3). One study in Malawi found a mortality rate of 16% in children with kwashiorkor (18). In that

study, 70% of mortality occurred during inpatient care, of which 53% occurred during the first four days of admission, suggesting that children had medical complications (also linked with high HIV prevalence). Nevertheless, mortality was also lower in the group with kwashiorkor (16%) compared to marasmic (47%) and marasmic kwashiorkor (42%). The comparative mortality rates in children with marasmus, kwashiorkor or marasmic kwashiorkor treated in outpatient care were reported in four studies *(6,18-20)* (Table 5). The mortality rates for children with kwashiorkor ranged from 0% to 4% and were consistently lower than those with marasmus (range from 4% to 5%) or marasmic kwashiorkor (range from 7% to 14%).

The comparison of the mortality rate in severely malnourished children treated in inpatient vs outpatient care after inpatient stabilization was reported in two studies from Malawi and Bangladesh (*14,15*) (Table 4). In Malawi, the mortality rate was 5.4% in inpatient and 3.0% for home-based therapy with RUTF. In Bangladesh, the mortality rate was 3.5% in inpatient, 5% in day care and 3.5% at home (after one week of day care). The higher mortality rate for inpatients in the Malawian study could have been associated with a higher incidence of infections for children who were hospitalized (fever, cough and diarrhoea; Wilcoxon's signed rank test, $p<0.001$ for all comparisons). The proportion of children with oedema in the two studies varied from 81% (Malawi) to 98% (Bangladesh), but their specific mortality rates were not reported. However, the mortality rate of a subgroup of children with oedema treated solely in outpatient care in the Malawian study was 4.0% and none of the children with oedema died after the transfer to domiciliary care in Bangladesh (personal communication of the author).

3.2.3 Weight/length/MUAC gain and recovery time

Five studies reported the mean or median weight gain in children with oedema treated in outpatient setting. This did not vary much and ranged between 2.7 g/kg/day and 4.0 g/kg/day *(5,6,14,17,19)* (Table 3). All those studies, except the studies in Bangladesh and Ethiopia, calculated weight gain during the first four weeks of treatment and did not specify whether this weight gain was registered after loss of oedema.

The median time to recover in outpatient care was only reported in two studies and ranged from 35 to 42 days (IQR 28–45) *(14,19)*. In one study, the median time to recover was comparable for kwashiorkor and marasmic cases and longer for marasmic kwashiorkor cases (*19*) (Table 5). However, the weight gain after loss of oedema was slower in the kwashiorkor group.

One study in Bangladesh compared the median time to recover in children treated in home care after one week of day care vs day care vs inpatient care (*14*). The group treated at home took significantly longer to lose oedema (respectively, 19, 13 and 11 days) and to recover (respectively, 35, 23 and 18 days) and the weight gain after loss of oedema was slower than in the other two groups (Table 4). It is important to highlight that there was no nutritional support for the group of children treated at home in this study. On the contrary, in the Malawian study (80% oedema) (*15*) the weight gain during the eight weeks of treatment was higher in the outpatient group treated with RUTF (3.7 g/kg/day) compared to the inpatient group (3.0 g/kg/day) (Table 4). This study calculated weight gain during the first four weeks of treatment (total duration of eight weeks) and did not mention whether weight gain was taken after loss of oedema in the subgroup of children with oedematous malnutrition.

Only three studies reported on mean length/height and MUAC gain in children with oedema treated in outpatient care (*5,6,17*) (Table 3). These were consistent and ranged for length/height gain between 0.24 and 0.39 mm/day and for MUAC gain between 0.2 and 0.3 mm/day. The rate of MUAC and length gain was higher in the outpatient group (with

distribution of RUTF) compared to the inpatients in one study with 80% oedema (*15*) (Table 4).

3.2.4 Costs

Only one study explored the cost per child for SAM treated in inpatient care vs day care vs home care after one week of day care and found that the latter was four times more cost effective than inpatient care (*13*) (Table 4). However, the parental costs were highest for domiciliary care as no food supplements were provided. No studies explored the cost per child for the specific group of children with oedema.

3.2.5 Adverse events

Default rates

The default rates for children with oedema treated in outpatient care were reported in six studies and varied between 3.6% and 15% (Table 3). In the study from Malawi with 15% drop-out, children were first treated in a tertiary hospital *(18)*. Another study in Bangladesh found the lowest defaulter rate in inpatient care (1%), followed by outpatient care (4%) and day care (17%) (*14*) (Table 4). In the group of children treated in outpatient care, all defaulters occurred during the first week of day care (personal communication of the authors). Defaulting appeared similar in the group of children with kwashiorkor (range from 1% to 15%) compared to marasmic children (range from 6% to 19%) (four studies; Table 5).

Infection rate

One study explored the prevalence of fever, cough and diarrhoea as secondary outcomes (*15*). The group of children who were managed in inpatient setting had twice the incidence of symptoms of infection during their recovery periods than the children in home-based treatment with RUTF. This could have influenced the outcome of inpatient vs outpatient treatment in this study and contributed to the higher mortality rate and lower recovery rate in the group of inpatients.

3.3 Quality appraisal

Table 6 summarizes the quality appraisal for the selected studies. Overall, the quality of the evidence was low. The definition of oedema was poorly or not defined in five of the eight studies. The precision and accuracy of anthropometric measurement was not addressed in most of the studies, which may influence the reliability of outcome measurements (recovery, weight/height/MUAC gain). Weight gain was sometimes measured during the first four weeks of treatment and it was not mentioned whether assessment was done after resolution of oedema (*5,6,17*).

4. Discussion

This systematic review did not retrieve direct evidence on the effectiveness of managing children >6 months with uncomplicated oedematous malnutrition grade +/++ in the outpatient vs inpatient setting as no study with a design appropriate to address such a question was retrieved. However, eight studies reported indirect evidence either by a comparison of outcomes in oedema cases treated in outpatient care after one week of institutionalized rehabilitation vs inpatient care, or case series of oedema cases treated in outpatient.

Among the uncomplicated cases of oedematous malnourished children treated exclusively in outpatient setting, recovery rates exceeded 87% and case fatality rates remained below 4%. The default rates remained below 10%, indicating that outpatient management is an acceptable option for the caretakers. These figures conform with the Sphere Guidelines and the Prudhon index for case fatality rate (*11,12*). One study exceeded the Sphere standards, but

data suggested that there were many complicated cases with high case fatality rates (also linked with high HIV prevalence) during the first four days of inpatient stabilization *(18)*. It is, however, quite difficult to disentangle from the reported results what part of this higher mortality can be attributed to either more severe cases at entry than in other studies, cross-infection during hospitalization or suboptimal inpatient care. Also in the study in Bangladesh the weight gain in children with oedema treated in outpatient care did not meet the minimum Sphere standards (*14*). The authors of that study suggested that this was due to the absence of food supplementation in the outpatient treatment group. It needs, however, to be highlighted that the procedure to assess weight gain was not uniform over the studies and that Sphere standards are not necessarily adapted to the specific group of children with oedema neither for outpatient treatment.

Only two studies allowed the comparison of outcomes for outpatient care vs inpatient care *(14,15)*. It is worth mentioning that the outpatient care occurred after one week of inpatient stabilization in both studies. In Ciliberto et al. results were much better in outpatient care than in inpatient care, and the higher infection incidence during rehabilitation in the former group was presented by the authors as an explanatory factor (*15*). In Khanum et al., the rehabilitation was longer and the recovery rate lower in outpatients than in inpatients, but as already explained above children in outpatient care did not receive food supplements (*14*). In five other studies (Table 6), the mortality rate was lower and the recovery rate higher in children with kwashiorkor than in children with marasmus or marasmic kwashiorkor.

These are encouraging findings indicating that severely malnourished children with oedema and no other medical complications can be effectively treated in outpatient care. However, caution is required before generalizing these results to any case of oedematous malnutrition for three reasons. First, the severity of oedema was poorly defined in all studies. The only three studies assessing the severity of oedema did so by measuring the depth of the thumb imprint on the dorsum of the foot, not by referring to the grading +/++/+++. Whether the good results observed across the studies included in this review relate to populations with a majority of cases presenting a mild oedema (grade +) is unknown, but the fact that the worst results were observed in studies where children underwent a first week of inpatient care might be an indication in that direction *(14,15,18)*. Conversely, worse outcomes in more severe oedema cases could have been masked by the reporting of mean values as none of the studies stratified their results by grade of oedema at entry. Second, differences in nutritional status between defaulters and remainders were not described in the majority of the studies. It is possible that defaulters were in worse condition than remainders, as suggested in two studies (*5,16*), and that their outcomes were also worse. Although the default rates were relatively low in most studies, these figures may add to death rates. Moreover, most studies were observational, and the presence of selection bias was difficult to assess, particularly in the retrospective case series *(19,20)*. It is striking that death rates were higher in the three trials *(14-16)* than in the observational studies, with the exception of the study by Sadler et al. *(18)*. Lastly, six of the eight studies had been carried out in Malawi where the prevalence of HIV is high and where the ratio kwashiorkor/marasmus in SAM children is potentially higher than in other settings. The external validity of the results is thus unknown, as the patho-physiology of oedematous malnutrition is still poorly understood and may vary in different regions.

There were also variations in the management procedures between studies. International guidelines recommend administration of antibiotics as part of the case management of SAM cases in outpatient (*10*). However, the systematic prescription of antibiotics occurred only in four of eight included studies *(14,15,18,19)*. Nevertheless, this did not seem to have an impact on the mortality and recovery rates. This coincides with the findings of a retrospective cohort study in which uncomplicated oedematous cases treated with amoxicillin did not have better outcomes for mortality and recovery than children who did not have routine antibiotics *(20)*.

No cost-effectiveness evaluation was included in our studies for the specific group of children with oedema treated in outpatient. However, a study in Bangladesh found that home-based treatment was four times lower than centre-based care and was preferred by mothers *(14)*. This result related at least partially to the fact that no food supplementation was provided to the outpatient group in that study. Another review highlighted the scarcity of experimental evidence on cost-effectiveness of CMAM and that more funding should be invested in rigorous evaluation of that parameter (21).

In conclusion, our review showed that oedematous malnutrition can be treated effectively in outpatient service. However, the quality of evidence was low and further good quality studies in various settings are required before conclusive guidance can be generated. Outpatient treatment of nutritional oedema already occurs in many programmes. A thorough evaluation of these programs would complement this review. Outcomes stratified by degree of nutritional oedema (+/++/+++) are particularly needed. This review also found that marasmic kwashiorkor patients had a higher risk of death and complications. These patients require intensive care, monitoring and cautious F-75 based feeding regimens of phase one therapeutic care that are not possible in outpatient treatment (*3*). This also emphasizes the need to combine indicators of SAM, in contradiction with the current WHO guidance of using WHZ, MUAC or bilateral pitting oedema independently (*1*). Future RCT should also include assessment of cost-effectiveness and coverage of the intervention.

Table 2

Characteristics of included studies reporting on outpatient treatment of oedematous malnutrition

Reference	Country	Period (month)	No. SAM	Prevalence of oedema (%)	Prevalence oedema and not wasted[a] (%)	Definition of oedema	Admission criteria	Intervention	Oedema direct outpatient (%)	Recovery criteria	Type of study
Amthor 2009 (*17*)	Malawi	5	826	99	71	Non-severe <1 cm pitting	6–60 months, W/H <70% and/or oedema and appetite	Outpatient, RUTF[b]	100	W/H ≥85% (8 weeks)	O
Ciliberto 2005 (*15*); Ciliberto 2006 (*6*)[c]	Malawi	7	645	81	NR	Mild <0.5 cm pitting	10–60 months, "mild" oedema and/or W/H <-3 SD and appetite (no complications if direct outpatient)	Second phase in inpatient therapy (n=113) vs home-based RUTF[b] after 1 week hospitalization (n= 532)	39	W/H >-2 (8 weeks) and oedema resolved (4 weeks)	Non-randomized (stepped wedge design[d]) controlled comparative trial
Collins 2002 (19)	Ethiopia	3.5	170	38	30	Present or absent	6–120 months, W/H ≤70% or oedema	Outpatient, RUTF 4.2 MJ/day and 24.3 g protein/d and Famix 8.26 MJ/d	100	W/H ≥85% and no oedema	O retrospective
Khanum 1994 (*14*); Ashworth 1996 (*13*)	Bangladesh	12	473	98[e]	15	Present or absent	12–60 months, oedema and/or W/H <60%	Inpatient (n=100) vs day care (n=200) vs home care after 1 week day care (n=173) No food supplementation in home care	0	W/H >80%	RCT with sequential allocation[f]
Linneman 2007 (*5*)	Malawi	12	2131	98	NR	Mild and moderate <1 cm pitting	6–60 months, SAM: oedema and/or W/H < 70% and appetite	Outpatient, RUTF[b]	77[g]	Oedema resolved and W/H >85%	O
Oakley 2010 (*16*)	Malawi	10	1874	78	67	Present or absent	6–59 months, SAM: oedema and/or W/H <-3SD and appetite	Outpatient, RUTF 25% milk (n=945) vs 15% milk (n=929)	100	W/H >-2 SD and no oedema 8 weeks	RCT, double blind
Sadler 2008 (*18*)	Malawi	12	1044	78	68	Present or absent	6–60 months, W/H <70% and/or oedema	Home-based RUTF 170 kcal/kg/d + family ration 700 kcal/d after inpatient stabilization	0	W/H >85%	O
Trehan 2010 (*20*)	Malawi	24	2453	80	NR	Present or absent	6–59 months, SAM: oedema and/or W/H <-3 SD and appetite, uncomplicated	Outpatient, RUTF[b] with 7 d amoxy (n=498) vs no amoxy (n=1955)	100	W/H >-2 SD and no oedema (4 weeks and 12 weeks)	O retrospective

No. = number; NR = not reported; O = observational

[a] Wasted defined by anthropometric measurement W/H <-3 SD, except in Ciliberto 2006 W/H <-2 SD.

[b] RUTF 175 kcal/kg/d and 5.3 g protein/kg/d for 8 weeks.

[c] 75% overlap in population with oedema treated exclusively in outpatient (personal note from author) (n=171 vs n=219).

[d] First three weeks of centre participation; only inpatient.

[e] 80% still had oedema at start of outpatient (personal note from author).

[f] Allocation to treatment group through daily rotation.
[g] Proportion of SAM following 8 weeks; outpatient RUTF.

Table 3
Outcomes of severely malnourished child with oedema treated in outpatient care

Reference	No. oedema	Mortality (%)	No death	Predicted No. death (*12*)	Recovery (%)	Median time to recover (d) (IQR)	Mean weight gain (g/kg/d) +/- SD	Mean length gain (mm/d) +/- SD	Mean MUAC gain (mm/d) +/- SD	Use of resources cost/child	Other adverse effects
Amthor Malawi 2009 (*17*)[a]	819	0.9	8	8	93.7	NR	2.7±3.7	0.3±0.9	0.2±0.3	NR	Default 3.6%, failure 1.8%
Ciliberto Malawi 2005 (*6,15*)	171	4[b]	8	30	89[b]	NR	2.8±3.2[b]	0.24±0.27[b]	0.3±0.4[b]	NR	Overall default 9.6%, relapse 3%
Collins Ethiopia 2002 (19)[c]	50	0	0	NR	96	42 (28–45)	2.7 (0.0–.8)[d]	NR	NR	NR	Transferred 0%, default 4%
Khanum 1994; Ashworth 1997 Bangladesh (*13,14*)[e]	170	3.5	6	NR	75	35 (NR)	4±NR	NR	NR	Institutional cost $29/child, parental cost $9/child	Default 4%, late exclusion[f] 17%
Linneman Malawi 2007 (*5*)[g]	2090	1	29	64	89	NA	3.5±4.1	0.39±0.54	0.24±0.35	NR	Default 7%, failure 3%
Oakley Malawi 2010 (*16*)[h]	1458	3.5	64	58	88	NR	NR	NR	NR	NR	Default 3%
Sadler Malawi 2008 (18)	731	16	117	NR	69	NR	NR	NR	NR	NR	Default 15%
Trehan Malawi 2010 (20)	1962	1.5	29	NR	87.7	NR	NR	NR	NR	NR	Default 8.3 %, failure 2.5

No. = number; NR = not reported; $ = United States dollar
[a] Outcomes of SAM (99% oedema).
[b] Outcomes for the group presenting oedema (kwashiorkor and marasmic kwashiorkor) and treated exclusive outpatient. Outcomes group oedema and no wasting in OTP (Ciliberto 2006): recovery 95%, mortality 4%, default 1%, failure 1%.
[c] Outcomes group oedema and no wasting in OTP.
[d] Median weight gain (IQR).
[e] Outcomes of SAM (98.5% oedema) in outpatient. 80% had oedema at start of home care; mortality 0%, recovery 100% in oedema and non-oedema cases.
[f] Due to tuberculosis or blood transfusion.
[g] Outcomes of SAM with oedema (98%) exclusively treated in outpatient (77%) were not reported separately.
[h] Mortality (4%), defaulting (3%), failure (8%) and transfer (2%) only reported for the global group (kwashiorkor or marasmus or both).

Table 4

Comparison of outcomes for different treatment approaches

Reference	Treatment	Mortality (%)	No. deaths	Predicted no. deaths (*12*)	Recovery (%)	Time to recover (d)	Weight gain (g/kg/d) ± SD	Length gain (mm/d) ± SD	MUAC gain (mm/d) ± SD	Cost/child ($[a]) institutional/ parental	Prevalence fever ± SD (d)	Prevalence cough ± SD (d)	Prevalence diarrhoea ± SD (d)	Relapse (%)	Relapse (6months)[b] (%)	Default rate
Ciliberto 2005 (*15*)	Inpatient	6.2	10	9	49	NR	3.0±8.8	0.04±0.35	0.28±0.44	NA	1.8±3.3[c]	1.8±3.6[c]	1.3±2.7[c]	10.6	39.1	8.1[b]
	Outpatient (1 inpatient)	3.7	30	30	72	NR	3.7±4.3	0.20±0.33	0.42±0.71	NA	1.0±2.0[c]	0.8±2.4[c]	0.7±1.7[c]	6.2	2.2	9.8[b]
Khanum 1994; (14) Ashworth 1997 (13)	Inpatient	3.5	7	NR	86.5	18	11	NR	NR	155.9/3.1	NR	NR	NR	NR	NR	1.0
	Day care	5.0	10	NR	67.0	23	6	NR	NR	59.3/4.5	NR	NR	NR	NR	NR	17.0
	Outpatient (1 day care)	3.5	6	NR	75.1	35	4	NR	NR	29.4/9.4	NR	NR	NR	NR	NR	4.0

No. = number; NR not reported

[a] United States dollar.

[b] Default rates in global study group of MAM and SAM.

[c] Wilcoxon's signed-rank test, $p<0.001$ for all comparisons.

Table 5

Comparison of outcomes of outpatient treatment in kwashiorkor – marasmic kwashiorkor – marasmus

Reference	Mortality (%)			Recovery (%)			Median time to recover (d) (IQR)			Weight gain (g/kg/d) +-SD			Defaulter (%)				Transferred (%)		
	M	K	MK	M	K	MK	M	K	MK	M	K	MK	G	M	K	MK	M	K	MK
Ciliberto 2006 (*6*)	NR	4	7	NA	95	65	NR	NR	NR	NR	NR	NR	4.0	NR	1	8	NR	NR	NR
Collins 2002 (19)	5	0	14	81	96	71	42 (28–56)	42 (28–45)	56 (42–70)	4.8[a] (2.9–8.1)	2.7[a] (0.0–4.8)	4.0[a] (2.7–4.3)	5	6	4	0	9	0	14
Oakley 2010[b] (*16*)	NR	NR	NR	70	88	NR	NR	NR	NR	NR	NR	NR	3	NR	NR	NR	NR	NR	NR
Trehan 2010 (20)	3.7	1.5	NR	75.1	87.7	NR	NR	NR	NR	NR	NR	NR	9	11.8	8.3	NR	NR	NR	NR
Sadler 2008 (18)	47	16	42	33	69	38	NR	NR	NR	NR	NR	NR	16.2	19	15	20	NR	NR	NR

M = marasmus, K = kwashiorkor; MK = marasmic kwashiorkor defined as oedema and wasted W/H <-3 SD, except for Ciliberto 2006 where wasted is defined as W/H <-2 SD; G = global malnutrition (M or K or MK); NR = not reported

[a] Median weight gain (IQR).

[b] Mortality (4%), defaulting (3%), failure (8%), weight gain (2.2 mg/kg/d), MUAC gain (0.15 mm/d), and transfer (2%) only reported for the global group.

Table 6

Quality appraisal studies reporting on outcome of children with oedema

Reference	Sources + methods of selection correctly described	Reliability of measures					Statistical analysis	Missing data			Other comments
		Training of assessors	Definition of oedema	Double measurement	Quality control (method)	Reference test[a]		Oedema assessed in all children	% drop-out	Differences of drop-outs assessed	
Amthor 2009	M	A	A	NR	NR	NR	P (median test, p)	NR	3.6	NR	Case series, Malawi (high HIV prevalence)
Ciliberto 2005; 2006	M	NR	A	NR	NR	NR	A, intention to treat analysis, difference in CI 95%	A	9.6	NR	Non-randomized controlled trial, Malawi, high HIV prevalence
Collins and Sadler 2002	M	A	NR	NR	A	NR	P, (χ2 for proportions)	A	5	NR	Retrospective, no inpatient facility available All oedema cases treated outpatient
Khanum 1994; Ashworth 1997	M	NR	NR	NR	NR	NR	NR	NR	9.8	NR	RCT with sequential allocation Main focus cost-effectiveness analysis
Linneman 2007	M	A	A	NR	NR	NR	NR	A	7.4	Drop-outs had lower anthropometric indices	Case series, Malawi (high HIV prevalence)
Oakley 2010	M	A	NR	A	A	A	A, Intention to treatment, Cox regression (M,K)	NR	3	Drop-outs were younger and more marasmatic	(RCT double blind, two types RUTF), Malawi
Sadler 2008	P	A	NR	NR	A	NR	NR	NR	15	A	Case series, initial inpatient, high HIV %
Trehan 2010	P	NR	NR	NR	NR	NR	A (for the assessment of the differences due to antibiotic)	NR	8.3	NR	retrospective, uncomplicated SAM and RUTF, all oedema cases treated outpatient

NR = not reported; M = moderate; A = appropriate; P = poor

[a] Results of index test were interpreted relative to the reference standard.

Annexes

Annex 1: Overview of 33 guidelines on CMAM

Country	Year	Oedema +/++ in outpatient?
Afghanistan	2008	Yes
Angola	2008	No
Bangladesh	2010	Yes
Botswana	2009	Yes
Burundi	2010	Yes
Central African Republic	unknown	Yes
Democratic Republic of the Congo	2008	Yes
Djibouti	2009	Yes
Ethiopia	2007	Yes
Eritrea	Extract with admission/discharge criteria - 2010	Yes
Ghana	2010	Yes
Honduras	Revisions without date	Yes
Côte Ivoire	2010	Only oedema +
Kenya	2008	Only oedema +
Madagascar	2009	Yes
Malawi	Draft without date	Yes
Mali	2007	No
Mauretania	2007	Yes
Mozambique	2010	No
Republic of Niger	2009	No
Rwanda	No date	Yes
Sierra Leone	2009	Yes
Somalia	2010	Yes
Republic of the Sudan	2009	Yes
Republic of South Sudan	2009	Yes
Sri Lanka	2007	Yes
Tanzania	2010	No
Tajikistan	2009	Yes
Togo	2009	Yes
Uganda	2010	Yes
Yemen	2008	Yes
Zanzibar	2010	No
Zimbabwe	2008	Yes

Annex 2

Key words used for database other than Medline

The key words used in:

- Cochrane library: “nutritional edema”
- Embase: “(((‘kwashiorkor’/exp OR (‘malnutrition’/exp AND ‘edema’/exp) OR (‘nutritional deficiency’/exp AND ‘edema’/exp) OR (wast* AND ‘edema’/exp)) AND (‘infant’/exp OR ‘child’/exp)) AND (‘community care’/exp OR treatment OR ‘rehabilitation’/exp OR ‘management’/exp OR ‘hospitalization’/exp)) NOT (‘editorial’/exp OR ‘letter’/exp OR comment)) ”,
- DARE: “kwashiorkor OR (nutrition AND edema)”

Annex 3
Studies excluded and reasons for exclusion

1.	Ashworth 2006 (22)	Review examining the effectiveness of 16 studies with community-based rehabilitation for treatment of SAM. Rehabilitation is referring to the second phase of treatment. No reporting on prevalence of oedema.
2.	Birem-Etchebes 1988 (23)	Intervention: All kwashiorkor and marasmic cases were hospitalized. Qualitative study. No data on main outcomes.
3.	Bredow 1994 (24)	45 children with severe, moderate or mild malnutrition (following the Gomez classification) followed in outpatient. Only four (9%) oedema and no reporting of outcomes of these children with oedema.
4.	Brown et al. 2009 (25)	Review on community-based management of SAM and moderate acute malnutrition (MAM). No reporting on prevalence of oedema.
5.	Chaiken 2006 (26)	No reporting of prevalence and outcomes of patients with oedema in outpatient.
6.	Chapko 1994 (27)	RCT: comparison of hospital vs day care. 24% oedema. No reporting of outcomes in patients with oedema.
7.	Collins 2006 (*3*)	Review on community based-management of SAM with RUTF. No reporting on prevalence of oedema.
8.	Diop 2003 (28)	Inclusion after oedema disappeared.
9.	Fernandez-Concha 1991 (29)	No reporting on prevalence of severely malnourished children with oedema, only 12 cases of third degree malnutrition (W/A).
10.	Gaboulaud 2007 (*8*)	Comparison of inpatient, inpatient followed by home treatment and exclusive home treatment. Cases of oedema were excluded from group with exclusive home treatment.
11.	Gossens 2012 *(30)*	Children with oedema were treated in in-patient setting
12.	Gueri 1985 *(31)*	No reporting on prevalence oedema, no data on main outcomes.
13.	Heikens 1989 *(32)*	Exclusion of oedema cases in outpatient.
14.	Husaini 1982 *(33)*	Very small sample (five children with kwashiorkor).
15.	Jansen 1986 *(34)*	Supplementary feeding at home. No reporting on prevalence oedema, no data on main outcomes.
16.	Kumari 1975 *(35)*	No data on main outcomes.
17.	Lapidus 2009 *(36)*	Moderately and severely malnourished children were treated in inpatient (complications), outpatient or inpatient followed by outpatient. Risk factor analysis for mortality. No data on prevalence and outcomes of patients with oedema in outpatient.
18.	Manary 2004 *(37)*	Intervention: Testing of three dietary regimens, all obtained initial inpatient stabilization (>80% oedema during hospitalization). No reporting of prevalence and outcomes of patients with oedema during outpatient phase.
19.	Manary 2008 *(38)*	Review on management of MAM and SAM. No reporting on outcomes.
20.	Ndekha 2004 *(39)*	Idem as Manary 2004, but with HIV positive children. All obtained inpatient stabilization (<80% oedema). No reporting of prevalence and outcomes of patients with oedema in outpatient.
21.	Prudhon 1997 *(12)*	Model to calculate the number of deaths based on nutritional status (including presence of oedema).
22.	Sandige 2004 *(7)*	Intervention: All obtained inpatient stabilization. 12% received exclusive outpatient. Percentage oedema and outcomes during outpatient phase is not reported.
23.	Sadler *(40)*	Evaluation of community-based treatment model of SAM. Prevalence of oedema 61%. Comparison between SAM with complications (78%) treated first in inpatient and those without complications treated indirectly in outpatient. Different triage criteria: Children with oedema ++/+++ were admitted in inpatient, children with oedema + in outpatient. The outcomes for children with oedema +/++/+++ were reported separately, but inconsistent with

		Collins 2006.
24.	Schoffield 1996 *(41)*	Review on causes of mortality in treatment of SAM.
25.	Shah 1971 *(42)*	Case report of 16 cases of Kwashiorkor. No data on main outcomes.
26.	Tellier 1996 *(43)*	No data on outcomes for SAM with oedema treated in outpatient.

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