Inpatient treatment of severe acute malnutrition in infants aged <6 months

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Executive summary

Background

Severe acute malnutrition (SAM) is a major global public health problem responsible for over one million young child deaths each year. Most focus to date has been on the management of SAM in children aged from 6 to <60 months. Growing evidence suggests that it is also a problem among infants aged <6 months. Of 20 million children under 5 years with SAM worldwide, 3.8 million are infants. To better manage and improve outcomes for infants aged under 6 months old (0–5.9 months) (infants <6m) SAM, a better evidence base regarding treatment for this group is needed. This review seeks to fill that evidence gap.

Methods

We carried out:

1. An Appraisal of Guidelines for Research and Evaluation (AGREE) of national SAM guidelines to determine what various countries are currently recommending in terms of infant <6m SAM treatment. AGREE is an international, standardized appraisal instrument to assess clinical management guidelines.

2. A Grading of Recommendations, Assessment, Development and Evaluation (GRADE) review of published literature to answer the following questions for inpatient treatment of infant <6m SAM:

- What is the safest and most effective therapeutic feeding strategy during stabilization phase treatment (which milk at what volume)?
- What is the safest and most effective therapeutic feeding strategy during the transition and rehabilitation phase of treatment?
- What is the most effective feeding protocol (time in each phase; progression criteria)?
- What is the most effective mode of therapeutic feeding (supplementary suckling [SS] or cupfeeding or spoon feeding)?

Results

AGREE appraisal of national SAM guidelines

Of 36 national SAM guidelines that were reviewed:

- 29 (81%) had specific sections focusing on infant <6m SAM; total page space of guidelines devoted to infants <6m ranged from 1% to 19%, mean 6%;
- all 29/29 guidelines recommended inpatient treatment – one distinguished between clinically complicated and uncomplicated SAM, as they do for older children;
- 28/29 guidelines recommended SS as the core treatment, the aim being to re-establish effective EBF.

As a group, the guidelines had many strengths: (i) clearly articulated scope and purpose (AGREE Domain 1); (ii) good professional stakeholder involvement (Domain 2); (iii) good clarity and presentation (Domain 4); and (iv) good tools to support applicability (Domain 5). Major weaknesses were: (i) lack of patient involvement; (ii) poor (or at least poorly expressed) rigour of development (Domain 3); and (iii) lack of clear editorial independence (Domain 6).

GRADE review

High-quality evidence for all of the key study questions was lacking; however, this presents both:

- a weakness since, by implication, all current guidelines are based on low-quality evidence;
- an opportunity since, by implication, there is equipoise and uncertainty around current recommendations, which creates great scope for research and future improvements.

Discussion and recommendations

Paucity of evidence has not prevented important country-level advances in guidance. Most countries now address infant <6m SAM – at least in their protocols. However, these current country-level approaches to infant <6m SAM are markedly out of step with current approaches to SAM in older children: there is no separation of complicated and uncomplicated infant <6m SAM; no outpatient based/public health focused model of care. Future research urgently needs to address this gap.

Current weak evidence should not hinder advances in international guidance on infant <6m SAM:

- the positive side of the current lack of gold standard evidence is that there is great equipoise on many issues and opportunity for future research;
- even just acknowledging infant <6m SAM would be a significant step forward and will stimulate future work in this area.

Specific guidance arising from this review on *nutritional aspects treatment* includes:

- Infants should be divided into two groups: those who do and those who do not have the potential to breastfeed (evidence LOW; recommendation STRONG).
- *Low-birth-weight (LBW) infants* should follow the World Health Organization (WHO) 2010 LBW guidelines (some of which may apply to SAM infants of unknown birth weight) (evidence LOW; recommendation WEAK).
- *AGE* should be considered during assessment and in treatment decisions.
- *For stabilization feeds*, there are several feed options. Infant formula at 100 kcal/kg/day is a strong option due to similarity with breast milk, low renal solute load and potential for lactose-free varieties (evidence LOW; recommendation CONDITIONAL – on availability of different feeds).
- *For transition and rehabilitation feeds*, again there are several possible options. For non-breastfed infants, breast-milk substitute (BMS) (formula or F-100) should be stepped up; for breastfed infants, it should be stepped down as breast milk is re-established (evidence LOW; recommendation CONDITIONAL).
- *Regarding the safest and most effective therapeutic feeding protocol*, the basic principles of slowly increasing feed volume for non-breastfed infants and re-establishing breastfeeding wherever possible are relatively clear. Exact details of how this should be done are not clear and should be left to local discretion (evidence LOW; recommendation CONDITIONAL - amount of detail needed depends on context).
- *Regarding the most effective mode of therapeutic feeding*, SS can be recommended for infants with the potential to breastfeed (evidence LOW; recommendation QUALIFIED – note low coverage; risk–benefit differences in some infants).

As well as optimizing and improving the evidence base around feeding treatment, future research and guidance should also focus on non-nutritional determinants of/influences on infant <6m SAM:

- clinical: e.g. HIV, tuberculosis (TB), disability, tongue tie, kangaroo care nursing, isolation nursing;
- carer-related: e.g. optimizing nutrition and fluid intake, especially for breastfeeding carers; better supporting mothers; better recognizing/addressing psychosocial issues.

There is potential for synergy by more closely linking nutrition and other health-care programmes.

With increasing evidence of the long-term as well as short-term impact of early nutrition and with early life nutrition now high on the political agenda, there has rarely been a better time to tackle infant <6m SAM.

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Conflicts of interest

None to declare.

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Abbreviations

AGREE	Appraisal of Guidelines for Research and Evaluation
ART	antiretroviral treatment
ARV	antiretroviral medication
BMS	breast-milk substitute
CI	confidence interval
CMAM	Community Management of Acute Malnutrition
EBF	exclusive breastfeeding
F-75	therapeutic milk used in stabilization phase of the treatment SAM
F-100	therapeutic milk used in transition and recovery phases of the treatment of SAM
F-100d	F-100 diluted
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HIV	human immunodeficiency syndrome
infant <6m	infant aged under 6 months old (0–5.9 months)
IU	international unit
IYCF	Infant and Young Child Feeding
LBW	low-birth-weight
MAMI	Management of Acute Malnutrition in Infants
MMI	maternal milk insufficiency
NGO	nongovernmental organization
PICO	Population, Intervention, Comparator and Outcomes
PRSL	potential renal solute load
NCHS	National Center for Health Statistics
NUGAG	Nutrition Guideline Advisory Group
RCT	randomized controlled trial
RUTF	ready-to-use therapeutic food
RR	risk ratio
SAM	severe acute malnutrition
SS	supplementary suckling
SUN	Scaling up Nutrition
TB	tuberculosis
UN	United Nations
WHZ	weight-for-height z-score
W/H	weight-for-height

W/L	weight-for-length
WHO	World Health Organization
WHO-GS	World Health Organization Child Growth Standards

Measurements

cm	centimetre
d	day
g	gram
h	hour
kcal	kilocalorie
kg	kilogram
kJ	kilojoule
l	litre
mg	milligram
ml	millilitre
n	number

1. Background

Severe acute malnutrition (SAM) is a major global public health problem responsible for over one million young child deaths each year (*1*). Over the last 10 years, significant progress has been made improving the management of SAM and scaling up the coverage and public health impact of treatment programmes. Efforts have largely focused on children aged over 6 months, whose treatment has been revolutionized by Community Management of Acute Malnutrition (CMAM) using ready-to-use therapeutic foods (RUTFs) (*2*,*3*). In contrast to this success, acute malnutrition among infants aged under 6 months old (0–5.9 months) (infant <6m) has often been sidelined both in terms of research and operational focus. This was recently highlighted by the Management of Acute Malnutrition in Infants (MAMI) project (*4*), a multiagency review of current evidence, policy, practice and programme outcomes for SAM infants <6m. Key findings from MAMI include the following.

- **Infant <6m SAM is a public health-scale problem**

  There was (and sometimes still is) a misconception that infant <6m SAM is rare. Because infants <6m have a target diet of exclusive breastfeeding (EBF), and because EBF provides optimal nutrition and protects against infections that can precipitate malnutrition, a false logic concludes that infants <6m are, therefore, rarely malnourished. Such reasoning ignores the fact that worldwide rates of EBF are strikingly low: only 25–31% among 2–5 months olds (*5*). It also ignores published estimates on infant <6m SAM (see below).

- **Prevalence of infant <6m SAM (and proportion of child SAM that is in infants <6m) will increase as World Health Organization Child Growth Standards (WHO-GS) are adopted worldwide** (*6*)

  Compared to the United States National Center for Health Statistics (NCHS) growth references, WHO-GS have lower thresholds for undernutrition among infants <6m (Figure 1). Using the current definition of severe wasting as weight-for-height <-3 z-scores (WHZ) (and thus omitting the contribution of oedematous malnutrition to SAM due to lack of data), of 555.5 million 0 to <60 month olds in developing countries worldwide:

  - of a total 9.3 million infants and children with SAM, 0.8 million (9%) are aged <6m (using NCHS growth references);
  - of a total 20 million infants and children with SAM, 3.8 million (19%) are aged <6m (using WHO growth references).

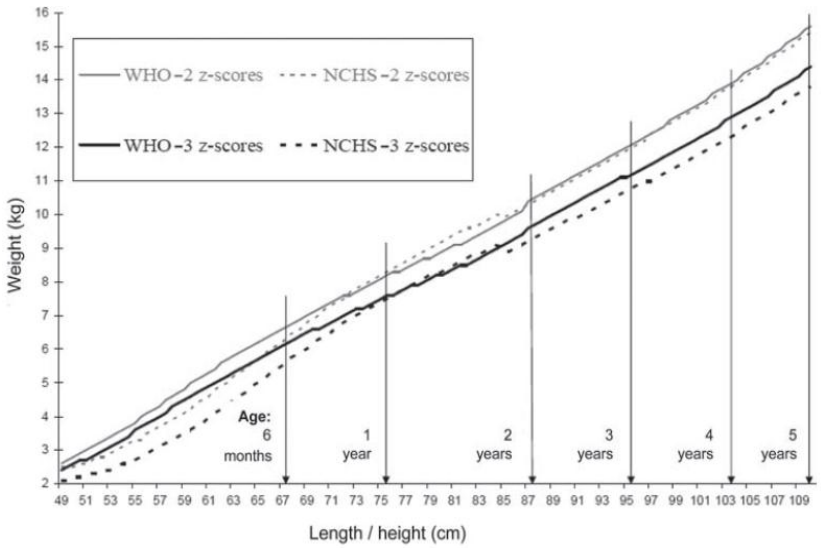


Figure 1

Difference in WHO and NCHS -2 and -3 z-score cut-offs[a]

[a] Arrows on the figure show median length/height at different ages for boys (using WHO-GS).

Source: Kerac et al. (*6*).

- **Treatment of infant <6m SAM is challenging**

  Due to recommendations on EBF for the first six months of life, infants <6m are not traditionally considered eligible for RUTF. Treatments are focused around trying to re-establish EBF wherever possible and are both time intensive and require especially skilled staff. Such resources are scarce in the settings where SAM is most prevalent. With consequent limited capacity, an unofficial "Don't Look/Don't See" policy sometimes operates whereby neither surveys nor treatment programmes proactively look for SAM in this age group. This is in contrast to active case finding and early detection that is a core feature of treatment strategies for older children.

- **Infant <6m mortality is high but the evidence base for treatment strategies is sparse**

  In MAMI's meta-analysis of available programme data, case fatality of infants <6m was significantly higher (RR 1.29, 95% CI 1.08 to 1.53) than that of children admitted to the same programme. This is not unexpected given the greater vulnerability of infants <6m and greater range of possible underlying or contributing pathologies. What is unknown, however, is whether any of these deaths represent excess mortality that could have been avoided with more efficacious or better delivered (more effective) treatments. As noted by the 2004 WHO consultation on severe malnutrition (which focused on dietary management of infant <6m SAM) (*7*), "the evidence based for defining the most advantageous formulations for feeding this age group remains weak".

Reflecting the many challenges and uncertainties regarding infant <6m SAM, the WHO 1999 guidelines for *"*Treatment of severely malnourished children*"* only allude to this age group. Infants <6m are covered by the guidelines aimed at "children *below 5 years*" but are only directly mentioned once: "Infants <6m should have 50 000 IU of vitamin A" (this is a reduced dose compared to older children).

To better manage infants <6m, it is important to improve the evidence base around this age group. This review contributes to that goal by exploring the evidence for current inpatient-based treatments for infants <6m. Since the issues of "which treatment" and "which admission/discharge criteria to and from treatment" are inextricably linked, it should be read together with a sister-document on "Admission and discharge criteria for the management of severe acute malnutrition in infants <6 months" (*8*).

2. Aim

To inform future guidelines by synthesizing current evidence about the inpatient treatment of SAM in infants <6m.

2.1 Review questions

i. What are country guidelines currently recommending for the treatment of infant <6m SAM?

ii. For inpatient treatment of infant <6m SAM:
- What is the safest and most effective therapeutic feeding strategy during stabilization phase treatment (which milk at what volume)?
- What is the safest and most effective therapeutic feeding strategy during the transition and rehabilitation phase of treatment?
- What is the most effective mode of therapeutic feeding? (supplementary suckling [SS] or cup feeding or spoon feeding)?
- What is the most effective feeding protocol (time in stabilization phase; time in transition; criteria for phase progression)?

3. Methods

This report comprises two distinct sections: a review of national SAM treatment guidelines regarding current recommendations for infants <6m; and a review of published literature on current admission/discharge criteria for this age group and associated outcomes using these criteria. We used this two-step approach since we felt it unlikely that published literature would yield sufficient high quality evidence for us to make strong recommendations about which admission and discharge criteria *should* be used. In this situation, it is important to understand which admission and discharge criteria *are* currently being recommended.

3.1 AGREE review of national guidelines

We reviewed available national guidelines on the management of SAM and extracted data on admission and discharge criteria for infants <6m SAM. We used the Appraisal of Guidelines for Research and Evaluation (AGREE) tool (www.agreecollaboration.org/pdf/aitraining.pdf) as a framework to rate the content and quality of the guidelines, which rates guidelines on a four-point Likert scale where 1 = poorest and 4 = best. There are six AGREE domains covering a total of 23 items. *Since the same guidelines were reviewed for the accompanying admission/discharge criteria review, the same AGREE scores and comments apply here – they are reproduced in this report for ease of reference, but readers should note that the text is the same.*

3.2 GRADE review of published literature

We used Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria (www.GradeWorkingGroup.org) to evaluate published literature on infant <6m SAM. This considers a number of different criteria in order to assess study methodological quality: type of study (observational vs randomized); relevant choice of study population; appropriate choice of interventions and outcomes; and methods for controlling for confounders. Subjectivity arising from possible conflicts of interest is also assessed.

3.2.1 Search strategy and the Population, Intervention, Comparator and Outcomes (PICO) framework

We systematically searched online databases to identify published studies from 1950 to 2011 on the treatment of infant <6m SAM. Databases included PUBMED, Cochrane and the WHO International Clinical Trials Registry platform. We included publications in any language. Being a recognized hub of grey literature on SAM, we also searched for non-peer reviewed articles published in *Field Exchange*, the journal of the Emergency Nutrition Network (www.ennonline.net/).

We applied the following PICO framework to identify relevant studies:

Population
Infants aged <6m with SAM
Data allowing, the following subgroups were reported on:

- infants aged 0–2months; 2–4months; 4–6 months;
- infants with access to breast milk/those without;

- oedematous SAM (kwashiorkor); non-oedematous SAM;
- HIV positive/HIV negative/HIV unknown;
- HIV endemic settings/HIV non-endemic settings.

Intervention

- milk at initiation of treatment: F-75; F-100d; breast milk substitute (BMS); BMS specific for premature infants; modified animal milk;
- milk at rehabilitation phase of treatment (options as above);
- feeding protocol (time in stabilization phase; time in transition);
- feeding route: SS/cup feeding/spoon feeding.

Control group outcomes

- breast milk (if accessible) or BMS;
- primary: mortality;
- secondary: weight gain; diarrhoea; restoration of effective exclusive or sustained breastfeeding; time to recovery; length gain nutritional recovery; reoccurrence of malnutrition.

Setting

- inpatient.

Inclusion criteria

- observational as well as randomized studies were eligible for review (due to paucity of randomized studies) – however, these are presented separately in GRADE review tables;
- studies that include infants <6m;
- studies that report details of treatment and treatment outcomes;
- studies in any language.

Exclusion criteria

- no otherwise eligible study was excluded on the basis of poor methodological quality; however, quality of each study was rated and documented and its results interpreted in light of its quality.

3.2.2 Search terms

Searches for questions a, b and c (common search since all intimately related):

a. What is the safest and most effective therapeutic feeding strategy during stabilization phase treatment? (which milk at what volume)?
b. What is the safest and most effective therapeutic feeding strategy during transition and rehabilitation phase of treatment?
c. What is the most effective feeding protocol (time in stabilization phase; time in transition; criteria for phase progression)?

"((Infant Nutrition Disorders) OR (wasting OR Wasting Syndrome[MESH]) OR (emaciation) OR (underweight) OR (malnutrition) OR (kwashiorkor) OR (marasmus) OR (marasmic kwashiorkor))"

AND

(milk OR milk*)

Limits – Humans

Searches for Question d:

d. What is the most effective mode of therapeutic feeding (SS or cup feeding or spoon feeding)?

(supplement* suck*) (because supplementary and supplemental are used interchangeably)

OR

(relact*) (because SS is the means by which relactation is achieved)

OR

"Cup fe*"

OR

"Spoon fe*"

Limits – Humans

4. Results

4.1. Summary of national SAM guidelines

4.1.1 Origin and date

We identified guidelines from 36 countries, most of which (28/36, 78%) were from Africa (Table 1).

Table 1

Country guidelines included in the AGREE review

UN Region	Country	Language	Date of protocol
Eastern Africa (n=13)	Burundi	French	2010
	Djibouti	French	2009
	Ethiopia	English	2007
	Kenya	English	2008
	Madagascar	French	2009
	Malawi	English	2010
	Mozambique	Portuguese	2010
	Rwanda	English	2010
	Tanzania	English	2010
	Uganda	English	2010
	Zambia	English	2009
	Zanzibar	English	2010
	Zimbabwe	English	2008
Middle Africa (n=2)	Democratic Republic of the Congo	French	2008
	Central African Republic	French	Not stated
Southern Africa (n=1)	Botswana	English	2009
Western Africa (n=10)	Burkina Faso	French	Not stated
	Côte d'Ivoire	French	2010
	Ghana	English	2010
	Guinea	English	2008
	Mali	French	2008
	Mauritania	French	2009
	Niger	French	2009
	Senegal	French	2008
	Sierra Leone	English	2009
	Togo	French	2009
Northern Africa (n=2)	Sudan	English	2009
	South Sudan	English	2009
Asia (n=6)	Afghanistan	English	2008
	Bangladesh	English	2008
	India	English	2006
	Pakistan	English	2005
	Sri Lanka	English	2007
	Tajikistan	English	2009
Middle East (n=1)	Yemen	English	2008
The Americas (n=1)	Honduras	Spanish	2004

4.1.2 Treatment overview

Of the 36 guidelines, 29 (81%) had specific sections on infant <6m SAM. A further two recognized this age group but did not go into detail, implying the existence of other documents that covered the issue in more depth.

Of the 29 guidelines that recognized infants <6m, space devoted to infants <6m ranged from 2% to 19% (mean 8%) of total page count, excluding annexes (1–19%, mean 6% including annex pages).

Of the 29 guidelines that recognized infants <6m:

i. *Location of care:*
- 29/29 (100%) recommended inpatient care;
- 16/29 (55%) noted a "breastfeeding corner" or similar separate location away from other children, dedicated to treating infants <6m.

ii. *Treatment aims:*
- 24/29 (83%) specified "improving or re-establishing EBF" (or similar) as the core treatment objective; the others did not specify an objective, but mostly implied the same.

iii. *Target population:*
- 0/29 (0%) made a distinction between "complicated" and "uncomplicated" infant <6m SAM (which they do for older children);
- 22/29 (76%) explicitly divided infants into two distinct groups:
  - those with a possibility to breastfeed;
  - those with no possibility of breastfeeding (e.g. orphans with no mother);
- 6/29 (21%) did not directly discuss what to do for infants with no possibility of breastfeeding:
  - one of these six justified this by saying that this scenario was very rare;
- 1/29 (3%) did not seem to recognize that there were infants with no possibility of breastfeeding – this protocol talked about relactation of other female carers, e.g. an aunt.

iv. *Core interventions:*
- 28/29 (97%) used SS as the core treatment methodology[1] for infants with the possibility to breastfeed; one referred to the use of a "cup, syringe or NGT [nasogastric tube]" for feeding infants <6m, which could indirectly imply SS;
- 1/29 (3%) noted kangaroo care[2] specifically for nursing infants <6m;
- 1/29 (3%) noted kangaroo care in treating hypothermia and implied that it can be used for all young children;
- 19/29 (66%) mentioned kangaroo care as treatment for hypothermia across all age groups – the other 8/29 (29%) did not mention kangaroo care anywhere in the protocol.

[1] This is a treatment whereby the infant continues to breastfeed, but receives "top-up" milk via a tube held alongside the nipple. The rationale is to supplement intake while simultaneously stimulating an increase in breast milk production. As breast milk production increases, the supplement is gradually withdrawn until breast milk alone is providing for sufficient growth.

[2] Kangaroo care is a method of nursing an infant skin-to-skin on the mother's chest so as to: ensure warmth; ensure easy access to the breast for feeding; promote mother–infant bonding. It was originally developed for LBW neonates and most evidence of its effectiveness is in that group.

4.1.3 Systemic treatments

Of the 29 guidelines that recognized infants <6m:

i. *Vitamin A:*

- 25/29 (86%) recommended vitamin A supplementation in their treatment protocol:
  - 23/25 (92%) recommended doses of 50 000 IU upon admission for infants <6m, 3 of these 23 stated exemption for oedematous SAM;
  - 2/25 (8%) recommend vitamin A supplementation be taken at week 4 or upon discharge, rather than upon admission.

ii. *Folic acid:*

- 26/29 (90%) recommended folic acid treatment:
  - 20/26(77%) specified a single dose of 2.5 mg upon admission;
  - 3/26 (12%) recommended a single 5 mg dose upon admission;
  - 3/26 (12%) recommended 5 mg on admission plus a daily 1 mg dose for the remainder of stay;
- 3/29 (10%) did not specify any folic acid supplementation.

iii. *First-line antibiotics:*

- 25/29 (86%) recommended first-line antibiotics to be given to all SAM infants <6m:
  - 13/25(52%) recommended amoxicillin;
  - 12/25(48%) recommended amoxicillin *and* gentamycin;
- 2/29 (7%) did not specify any antibiotic treatment;
- 2/29 (7%) recommended giving antibiotics *only* if an infection is present.

Of the 25 guidelines recommending amoxicillin antibiotics, dose regimes vary widely:

- 13/25 recommended 30mg/kg x 2 per day (= 60mg/kg total over 24hours);
- 4/25 recommended 50mg/kg x 2 per day (= 100mg/kg total over 24hours);
- 4/25 recommended 20mg/kg x 3 per day (= 60mg/kg total over 24hours);
- 2/25 recommended 15mg/kg x 3 per day (= 45mg/kg total over 24hours);
- 1/25 recommended 20mg/kg x 2 per day (= 40mg/kg total over 24hours);
- 1/25 recommended 25mg/kg x 3 per day (= 75mg/kg total over 24hours).

iv. *Second-line antibiotics:*

- 6/29 (21%) specified a second-line antibiotic:
  - 1/6 (17%) recommended chloramphenicol;
  - 5/6 (83%) recommended gentamycin in addition to amoxicillin.

v. *Antimalarial:*

- none of the guidelines explicitly recommended an antimalarial treatment for infants <6m;
- 4/29 (14%) referred to national guidelines on use of antimalarials;
- 1/29 (3%) specified that antimalarials are not to be given to infants weighing less than 5 kg.

vi. *Iron:*

- 23/29 (79%) recommended ferrous sulphate supplementation to be administered via F-100d:
    - 19/23 (83%) also specified that ferrous sulphate should not be given until the infant has "improved" or is "suckling well";
- 6/29 (21%) made no specific recommendation regarding iron supplements for infants.

vii. *Other:*

- 1/29 (3%) stated that deworming medication should not be given as routine to infants <1 year;
- 1/29 (3%) emphasized the need to monitor for hypothermia and hypoglycaemia in infants <6m.

4.1.4 Feeds – for infants with the possibility to be breastfed

For infants who have the possibility to be breastfed, of the 29 guidelines that recognized infants <6m:

i. *Details of recommended breastfeeding regime (frequency, timing and other details):*

- 3/29 (10%) did not specify details of a breastfeeding regime;
- 26/29 (90%) recommended breastfeeding take place every three hours for at least 20 minutes (no variation of this recommendation was found):
    - 17/29 (59%) also specified that breastfeeding should occur more often if the infant is willing;
    - 10/29 (34%) suggested giving BMS 30–60 minutes after breastfeeding;
    - 11/29 (38%) suggested giving breast milk substitute one hour after breastfeeding.

ii. *BMS to be used in phase 1:*

- 28/29 (97%) recommended using F-100d, of which:
    - 14/28(50%) further specified that in the case of oedematous SAM, F-75 should replace F-100d;
    - 1/28 (4%) suggested that infant formula and F-100d be used interchangeably;
    - 1/28 (4%) suggested using F-100d or F-75;
- 1/29 (3%) stated always using F-75 only for infants <6m.

iii. *BMS frequency in stabilization phase (phase 1):*

- 28/29 (97%) recommended giving BMS eight times per day;
- 1/29 (3%) did not specify frequency.

iv. *BMS volume in stabilization phase (phase 1):*

- 23/29 (79%) stated that 130 ml/kg/day be given, equating to 100 kcal/kg per day;
- 3/29 (10%) suggested giving 135 ml/kg/day, also equating to 100 kcal/kg/day;
- 2/29 (7%) gave tables where volume per kg varies with weight, however, this too equates to a very similar number of kcal per kg per day;
- 1/29 (3%) recommended 110 kcal/kg/day.

v. *Rehabilitation phase feeds:*

- 23/29 (79%) explained that F-100d should be decreased to 50% of maintenance amount once the infant is gaining 20g/day, which should allow for the shift from BMS to EBF – most of these guidelines also stated that BMS should stop entirely if the infant continues to gain more than 10 g/day during the rehabilitation phase;

- 3/29 (10%) suggested that F-100d be decreased by one third once the infant is gaining 20 g/day;
- 1/29 (3%) suggested a more gradual decrease to 75% of maintenance amount once the infant is gaining 20g/day, followed by a decrease to 50% some days later;
- 1/29 (3%) stated that F-100d be decreased by 50% on day 15 of treatment;
- 1/29 (3%) did not give details of the rehabilitation phase.

vi. Definition of cure:

- 27/29 (93%) explained that infants may be discharged once they are gaining weight on EBF, regardless of the infant's weight-for-length (W/L):
  - 12/27 (44%) specified that the infant should be gaining weight in this way for five days before discharge;
- 13/29 (45%) expressed the need for inpatient treatment time to be "as short as possible" in order to reduce exposure to infections;
- 25/29 (86%) recommended that breastfeeding practices be well-established and checked before the mother and infant are discharged.

4.1.5 Feeds – for infants without the possibility to be breastfed

Of the 29 guidelines that recognized infants <6m, 22 (76%) presented a specific protocol for infants without the possibility to be breastfed:

i. BMS to be used in phase 1:

- 21/22 (96%) stated that F-100d be used as a BMS for infants without the possibility of breastfeeding, of these 21:
  - 19/21 (91%) also stated that F-75 be used in place of F-100d for oedematous infants;
  - 1/21 (5%) recommended that F-100 *and* "modified goats milk" should be given to infants without the possibility of breastfeeding;
- 1/22 (3%) suggested that F-75 be used as the BMS for these infants.

ii. BMS frequency in stabilization phase (phase 1):

- 20/22 (91%) recommended feeding eight times per day;
- 1/22 (5%) recommended feeding 8–12 times per day;
- 1/22 (5%) recommended F-75 but did not specify details of feed frequency.

iii. BMS volume in stabilization phase (phase 1):

- 13/22 (59%) recommended giving 130 or 135 ml/kg/day, equating to 100 kcal/kg/day;
- 8/22 (36%) provided a table with varying volumes per kg depending on weight;
- 1/22 (5%), the protocol recommended F-75 but did not specify the amount of BMS.

iv. Rehabilitation phase feeds:

- 20/22 (69%) explained that during the rehabilitation phase infants need F-100d in an increased amount to phase 1:

- 8/20 (40%) specified that F-100d should be doubled to 200 kcal/kg/day (of which one noted that the amount should be 150–220 kcal/kg/day);
- 7/20 (35%) specified that F-100d should be increased by 50% during this phase;
- 2/20 (10%) specified that F-100d should be increased by 30% during this phase;
- 2/20 (10%) recommended a progressive increase in milk volume;
- 1/20 (5%) noted that feed should be given at 130 ml/kg/day;

- 1/22 (5%) talked about switching from F-75 to F-100d for oedematous infants;
- 1/22 (5%) did not specify details.

v. *Definition of "cure":*

There were several subtly different recommendations:

- 6/22 (27%) when the infant has increased their original weight by 15%:
  - of which one mentioned it should be for two consecutive weeks;
- 1/22 (5%) when the infant has increased their original weight by 15–20%;
- 1/22 (5%) when the infant has increased their original weight by 20% or weight-for-length >-1 z-scores (WLZ);
- 6/22 (27%) when the infant reached more than 85% of median for W/L:
  - of which one noted more than 80–85% of median W/L;
- 3/22 (14%) when the infant reached more than a WHZ -1;
- 3/22 (14%) when the infant reached more than a WHZ -2;
- 1/22 (5%) discussed switching from F-75 to F-100d once oedema ended;
- 1/22 (5%) did not specify details.

4.1.6 Preparation for discharge and support for carers

Of the 29 guidelines that recognized infants <6m:

i. *Preparation for discharge (general):*

- 2/29 (7%) recommended checking that infants' immunizations are up-to-date before discharge;
- 15/29 (52%) recommended that the mother/carer be adequately counselled on health, nutrition, breastfeeding, parenting or similar before discharge;
- 5/29 (17%) recommended that infants receive play therapy or stimulation before discharge;

- 12/29 (41%) did not specify any particular preparations for discharge.

ii. Maternal diet:

- 26/29 (90%) recommended that the mother should:
    - drink at least 2 litres of water per day;
    - eat 2500 kcal per day;
    - take vitamin A supplements of 200 000 IU if the infant is <2m;
- 1/29 (3%) stated that the mother should receive cereal and vitamin supplements;
- 1/29 (3%) recommended "sufficient feeding" for the mother.

iii. Maternal (carer) psychosocial issues:

- 27/29 (93%) provided recommendations for the mother's psychosocial health, commonly suggesting the mother be "supported" and "reassured" and that staff should "be attentive" and explain all aspects of the treatment;
- 2/29 (7%) emphasized that special care is needed for depressed or traumatized mothers.

iv. Other issues related to carer:

- 3/29 (10%) specified the use of peer support (i.e. other mothers) to explain the SS technique;
- 1/29 (3%) presented a table summarizing some possible physical or psychosocial difficulties that a mother may experience.

4.1.7 HIV

Of the 29 guidelines that recognized infants <6m:

- 22/29 (76%) referred to treatment of HIV, but none referred specifically to infants <6m, instead there is a separate section for all children with SAM with underlying HIV. Details of HIV mentioned in the guidelines include:
    - consideration that lactose intolerance is common in HIV positive children;
    - HIV should be treated as per international guidelines on prevention of mother-to-child transmission;
    - antiretroviral medication (ARV) and antibiotic considerations that HIV positive SAM children should receive amoxicillin in addition to co-trimoxazole;

- recognition that there is a risk of tuberculosis (TB) coinfection;
- recommendation that HIV positive mothers should attend consultations on "children at risk" and "chronic disease management";
- recommendation in one guideline that breast milk of HIV positive mothers be heat treated.

- 3/29 (10%) briefly noted HIV but did not go into detail;
- 4/29 (14%) did not mention HIV.

4.1.8 Follow-up

Of the 29 guidelines that recognized infants <6m:

i. For infants:

- 20/29 (69%) recommended infant follow-up:
  - 4/20 (20%) recommended follow by a community health worker or social worker;
  - 3/20 (15%) recommended that infants have monthly follow-up visits;
  - 3/20 (15%) noted greater detail of follow-up procedures such as "fortnightly for two months and monthly thereafter for four months";
  - 10/29 (34%) emphasized the importance of follow-up visits but give no details.

ii. For carers:

- 21/29 (72%) recommended that the mother be enrolled in a "supplementary feeding programme" following discharge, usually with the caveat "if available";
- 8/29 (28%) did not specify a "supplementary feeding programme" or food rations or other specific follow-up for the mother.

4.1.9 Infant and Young Child Feeding (IYCF) issues

Of the 29 guidelines that recognized infants <6m:

- 7/29 (24%) mentioned IYCF, either directly or indirectly:
  - 3/7 (42%) mentioned IYCF as part of community health worker education topics;
  - 2/7 (29%) mentioned IYFC as a reference for further information on nutrition counselling/education;

- 1/7 (14%) referred to IYCF as part of the national health promotion campaign;
- 1/7 (14%) showed detailed tables on key messages related to breastfeeding, child nutrition and growth.

4.2 Appraisal of national SAM guidelines – guideline quality

The 29 guidelines that included infants <6m were rated according to the AGREE framework. Since the overall "package" of infant <6m recommendations was considered rather than isolated sections of it, the results are the same as in the sister review on admission/discharge criteria for infants <6m. They are *not* reproduced here in order to minimize the length of this report. Please refer to said report for details.

4.3 GRADE review of published literature

4.3.1 Question 1: What is the safest and most effective therapeutic feeding strategy during stabilization phase treatment (which milk at what volume)?

A 2009 randomized control trial (RCT) from the Democratic Republic of Congo (*9*) used standard admission and discharge criteria as already identified by the AGREE section of this review:

- admission: <70% W/L (NCHS) *or* infant too weak or feeble to suckle effectively *or* mother reports breastfeeding *or* mother reports that infant is not gaining weight at home;
- discharge: gaining weight (10 g/day for three to five consecutive days on breastfeeding).

The RCT recruited 161 infants and compared the efficacy of F-100d in non-oedematous infants <6m with a standard generic formula. No differences in weight gain or total duration of treatment nor on treatment outcome (death, recovery, default) were found.

Lactose intolerance

A 2010 study of 196 children with SAM and diarrhoea (aged 3–60 months with no separate infant <6m subanalysis, hence not included in the main review) admitted to a nutrition rehabilitation unit in Uganda found that 25.5% of them had evidence of lactose intolerance (stool reducing substance ≥1 + [0.5%] and stool pH <5.5) (*10*). Prevalence was highest (68%) in the age group 3–12 months, so presumably would have been high in infants <6m. Other factors associated with intolerance on bi-variate analysis included lack of up-to-date immunization, persistent diarrhoea, vomiting, dehydration and abdominal distension; EBF for less than four months and worsening of diarrhoea on initiation of therapeutic milk.

A 2002 RCT of 180 aboriginal children aged <3 months (again no separate infant <6m subanalysis, hence not graded) admitted with acute diarrhoea and/or malnutrition tested three intervention milk formulas (*11*):

- De-Lact, a low-osmolality lactose-free formula;
- O-Lac, a lactose-free formula;
- Alfare, a partially hydrolyzed formula.

The duration of diarrhoea in days (mean; 95% confidence interval) was significantly longer on Alfare (8.5; 7.0–10.0) compared to De-Lact (6.1; 5.0–7.2) and O-Lac (6.9; 5.6–8.1; p = 0.04). There were no

differences in mean intake between formulas, but palatability of Alfare was significantly worse ($p<0.01$) than the other formulas. Over the five-day trial, improvement in likelihood ratios was significantly greater ($p = 0.05$) for De-Lact (18.6; 10.6–26.6) than for Alfare (8.5; 2.1–14.9). Weight gain was not significantly different between the three formulas, except in a malnourished subgroup that had better weight gain on De-Lact ($p = 0.05$).

The authors concluded that "in these Aboriginal children with diarrhoea and growth failure, a low osmolality milk was associated with better outcomes".

Addition of nucleotides to formula milk

A 2004 Mexican study (*12*) of 12 marasmic infants aged 3–18 months (again no infant <6m subanalysis, hence not graded) fed them through a nasogastric tube with infant formula (3.35 kJ/ml) for two weeks and ad libitum for an additional two weeks. Anthropometric measurements and immunologic indicators such as phagocytosis, microbicidal activity, chemotaxis and cell proliferation index were determined. The sample was divided into two groups: group 1 (n=6) was fed formula with nucleotides added, while group 2 (n=6) was fed a formula with no nucleotides. Comparison of immunologic indicators showed no significant difference between groups. Both showed improvement in phagocytosis and microbicidal activity and group 2 additionally showed improvement in cell proliferation index. The authors concluded that: "infant formula with intake of 837 kJ/kg/day (200 kcal/kg/day) and proteins of 4 g/kg/day in infants with protein-energy malnutrition had a favorable impact on immunologic indicators regardless of addition of nucleotides.

4.3.2 Question 2: What is the safest and most effective therapeutic feeding strategy during transition and rehabilitation phase of treatment (which milk at what volume)?

No articles specifically comparing feeds in transition and rehabilitation were found. The Wilkinson RCT is still relevant to this question since the two feed arms continued as per standard protocols throughout transition and rehabilitation.

4.3.3 Question 3: What is the more effective feeding protocol (time in stabilization phase; time in transition; criteria for phase progression)?

A 2009 study from Bangladesh compared a phase WHO protocol with an unphased local version. Details of exactly what treatments infants <6m were given are not specified but weight gain under the two protocols was not statistically different (*13*).

4.3.4 Question 4: What is the most effective mode or therapeutic feeding (SS or cup-feeding or spoon feeding)?

For this question, the RCT noted in question 1 is relevant, though it compared feeds rather than mode of feeding, so it is effectively a cohort study for question 4.

A 2008 cohort study of SS in Afghanistan examined outcomes on 94 children admitted with a variety of admission criteria (*14*):

- infant <6m SAM (oedema, n=8; weight-for-height (W/H) <70% [NCHS], n=21);
- age <6 months and weight <4 kg, n=6;
- length <49 cm and age <6m, n=27 (note that NCHS growth references only went down to length 49 cm, hence this groups' W/L median could not be assessed);
- moderate malnutrition (70–80% median W/L) *and* maternal milk insufficiency (MMI), n=26;
- no malnutrition but MMI, n=3;
- MMI but anthropometric status unknown, n=3.

For each of the above groups, cure and death were the main outcomes determined. Overall, cure was 61/94 (64.9%) and deaths were 7/94 (7.4%). As well as having small numbers in each group – with high consequent risk of both bias and confounding – an additional problem in this study was heterogeneity in the definition of cure. Whereas centre protocols define cure as "discharge on breastfeeding alone", it emerged that only 16/55 (29%) of "cures" fully met this criterion. Some of the centres in the study were (wrongly) discharging children with milk supplements given to take home.

A 2000 study of SS recruited 25 infants using the following criteria (*15*):

- admission – <70% W/L (NCHS);
- discharge – once >85% W/L and four days on EBF.

Following these criteria and with SS as the main treatment, 16 (64%) infants were successfully discharged and 5 had to be referred to the local hospital.

Other relevant references

A WHO 1998 report "Relactation: Review of experience and recommendations for practice" outlined extensive evidence, albeit few RCT-type studies were included.

No references to cup feeding or spoon feeding in the SAM context were found, though there were plentiful references showing effectiveness in other settings, mostly showing no advantage over bottle feeding (*16–20*) (but equally no disadvantage). In SAM settings, the latter is most important since bottles are dangerous given how hard it is to keep them clean in resource-poor tropical settings.

5. Discussion and conclusions

5.1 Overview

Drawing on evidence presented in this review and citing other key references, this section summarizes:

- "Existing recommendations/practices" – Where are we now?
    - in terms of what current *national* guidelines are currently recommending (note again that the WHO 1999 guidelines have essentially no recommendations on infant <6m SAM);
- "Proposed recommendations/practices" – Where do we want to be in the future?
    - in light of evidence referenced in this report and other associated literature;
    - where appropriate, several possible options are given for consideration;
- What is the key evidence and what are the key issues underpinning proposed change?

5.1.1 Risk–benefit issues for the treatment of infants <6m

As with any intervention, considering the possible risks of a treatment is as important as considering its benefits. Whether it can be recommended depends on the balance of benefits and risk. This is particularly important for SAM in infants <6m. Whereas for older children, treating SAM has a good evidence base showing clear benefit balanced against negligible risk (notably if treatment is community based with RUTF) (*21*,*2*), the risk–benefit balance for infants <6m is more uncertain. In particular, inpatient admission, which is universally recommended for this age group, has potentially high costs (e.g. to the family in terms of opportunity costs; to the health system) and high risks (e.g. nosocomial infection). There also have been concerns expressed (albeit with much more evidence needed on this issue) about the possibility that labelling an infant as "malnourished" might interrupt rather than support EBF (*22*,*23*). See information summarized in Tables 2–12.

5.2 Risk–benefit summary tables and recommendations arising

As clear from section 4.2 (AGREE Appraisal of National SAM Guidelines), there are a large number of individual interventions suggested for infants <6m. The original scope of this review was to focus on details of nutritional treatment/feeding regime. However, other aspects of treatment cannot be ignored. But neither can they all be explored in detail: some (e.g. HIV treatment, vitamin A) are covered by other reviews in the Nutrition Guideline Advisory Group (NUGAG) series; others have no direct evidence available (e.g. evidence for kangaroo care focuses on its use in premature neonates rather than infants admitted from the community with SAM); others are simply beyond the scope of this review (e.g. which antibiotics are most appropriate for infants <6m).

Drawing together diverse issues that have emerged, the following system was thus used:

- treatment approach – inpatient vs outpatient treatment of infant <6m SAM (section 5.2.1);
- clinical interventions for inpatient infant <6m SAM (section 5.2.2);

- social/carer-focused interventions for infant <6m SAM (section 5.2.3);
- nutritional interventions for infant <6m SAM (sections 5.3.1–5.3.4 covered separately since it was the original focus of this review – also corresponding to the results sections 4.3.1–4.3.4).

5.2.1 Treatment approach – inpatient vs outpatient treatment of infant <6m SAM

This issue underpins the whole risk–balance dynamic of infant <6m treatment. If lower risk, lower cost outpatient-based treatment options were available for uncomplicated infant <6m SAM, then:

- admission criteria could be made more sensitive, which would likely compromise specificity – but, with a lower risk and lower cost treatment, this trade-off is more acceptable;
- greater population coverage (and consequent greater public health impact) of treatment programmes would be more easily achievable.

Table 2

Risk–benefit summary table for inpatient vs outpatient treatment of infant <6m SAM

Existing recommendation/practice All infants <6m with SAM are treated as inpatients with no distinction between complicated and uncomplicated infant <6m SAM.
Proposed recommendation/practice **Option 1** Continue to actively promote inpatient care as the *only* treatment option for infant <6m SAM. **Option 2** Make recommendations on inpatient care but *do not block* other approaches (i.e. focus on inpatient care but leave scope for local interpretation of the evidence, as best fits local context). **Option 3** Make recommendations on inpatient care but *actively* recommend that settings with the capacity for good quality *operational research (i.e. high quality monitoring and evaluation systems, able to detect any problems)* harmonize their approach to infant <6m SAM with that for older children, distinguishing between: • complicated SAM – continuing treatment in inpatient settings using current protocols; • uncomplicated SAM – that could be treated on an outpatient basis through provision of community-based interventions such as breastfeeding support groups/empirical antibiotics.

Quality of evidence (for outcomes deemed critical)	Low There is currently an absence of evidence showing that outpatient-based treatment is effective and safe; equally, however, there is also no evidence that inpatient care is necessary for all infants <6m with SAM.
Benefits/desired effects (of the complicated/uncomplicated approach to infant SAM)	**Option 1** (only allow inpatient-based care): • most conservative option; • most consistent with current national guidelines; • effective inpatient care will always be needed: even if classifications change, some infants <6m will always have complicated SAM. **Option 2** (do not block outpatient care where appropriate): • trade-off between the two extremes of options 1 and 3. **Option 3** (actively encourage outpatient care where appropriate): • increased programme capacity to treat infants <6m; • with greater capacity, greater scope for active case finding; for greater programme coverage; for greater public health impact; • lower cost per patient (assuming that outpatient costs are lower than inpatient costs); • research and quicker progress encouraged.
Risks/undesired effects	**Option 1** (only allow inpatient-based care): • limited programme capacity, coverage and limited public health impact; • potentially discourages operational research and slows progress. **Option 2** (do not block outpatient care where appropriate): • trade-off between the two extremes of options 1 and 3. **Option 3** (actively encourage outpatient care where appropriate): • safety still is not established for outpatient-based care; • details of the package of outpatient-based care not yet clear; • total programme cost could be greater if more patients are treated.
Values/acceptability	**Option 1** (only allow inpatient-based care): • could be the most acceptable given it is the current status quo; • if programme coverage is shown to be low, ethical dilemmas about knowingly leaving patients untreated. **Option 2** (do not block outpatient care where appropriate): • trade-off between the two extremes of options 1 and 3. **Option 3** (actively encourage outpatient care where appropriate): • without good evidence of safety and effectiveness likely to be challenged by health professionals, as originally happened with CMAM; • carers likely to value outpatient-based care and more likely to present *more* readily for care at an earlier stage of illness – due to lower opportunity costs of programme attendance.
Costs	**Option 1** (only allow inpatient-based care): • scale-up of inpatient care is likely to be cost intensive since it requires both inpatient time and specialists. **Option 2** (do not block outpatient care where appropriate): • trade-off between the two extremes of options 1 and 3. **Option 3** (actively encourage outpatient care where appropriate): • if programme coverage increases with outpatient care, then total cost may increase even if cost per patient (cost-

	effectiveness) improves.
Feasibility	**Option 1** (only allow inpatient-based care): • within current staff and space capacity constraints, the easiest option; • scale-up could prove challenging if programme capacity exceeded. **Option 2** (do not block outpatient care where appropriate): • trade-off between the two extremes of options 1 and 3. **Option 3** (actively encourage outpatient care where appropriate): • outpatient care for infants <6m is feasible but when first piloted will require high quality technical/logistical inputs to demonstrate safety.
Final recommendation	Option 2
Strength of recommendation	*Strong **OR** Conditional **OR** Qualified **OR** Weak* Qualified (any settings that do choose to adopt non-inpatient care need good quality monitoring and evaluation to ensure good outcomes – as in option 3).
Quality of evidence that informs recommendation	*High/Moderate/Low/Very Low* Low
Comments justifying recommendation	Using a case definition of WHZ <-3 (WHO growth references), 3.8 million infants <6m worldwide have SAM (of a total 20 million 0 to <60 month olds with SAM globally). This is a large increase over numbers defined by previous NCHS growth standards (0.8 million infants of a total 9.3 million 0 to <60 month olds with SAM) (*6*). The MAMI project clearly highlighted that many programmes struggled to deal with relatively small numbers of infant <6m SAM. To cope with the increased numbers defined using WHO-GS, a radical shift in approach is necessary. It is also necessary because inpatient-only treatment is an increasing anomaly in a world that recognizes the difference between complicated and uncomplicated SAM. It is important to recognize that inpatient-based care is itself associated with risk (e.g. nosocomial infection; interruption of EBF) so the current model of care should not be assumed to be automatically more or less safe than the proposed complicated/uncomplicated model of care.
Gaps, research needs, comments	Safety, effectiveness and cost-effectiveness of the following need to be tested in a variety of settings: • case definitions for uncomplicated infant <6m SAM; • different packages of outpatient-based care for uncomplicated infant <6m SAM.

5.2.2 Clinical interventions for infant <6m SAM

Many problems can underlie infant <6m SAM. Some pathologies (e.g. complex congenital heart disease; metabolic disease) are fatal if untreated. Even in developed country settings they pose significant diagnostic and management challenges. One useful classification of factors underlying a failure to thrive in infancy is provided by the textbook *Essential Pediatric Gastroenterology, Hepatology and Nutrition* (McGraw Hill 2005):

- inadequate intake (e.g. feeding mismanagement; inability to feed optimally – developmental delay, cleft palate, cerebral palsy); diencephalic syndrome);
- inadequate absorption of nutrients (e.g. pancreatic insufficiency (cystic fibrosis, Schwachman-Diamond syndrome);
- excessive loss of nutrients (e.g. vomiting – central nervous system abnormality; intestinal obstruction; metabolic abnormality; gastro-oesophageal reflux); protein-losing enteropathy; chronic diarrhoea;
- excessive requirement (e.g. chronic illness – cystic fibrosis; congenital heart disease; inflammatory bowel disease); thyrotoxicosis; chronic infection (e.g. TB, HIV); malignancy; burns.

This list is not exhaustive, but it does make the point that focusing on breastfeeding problems alone will not solve infant <6m SAM in all cases. Both at outset and especially if standard nutritional care is failing to effect cure, it is vital to consider whether there could be other underlying problems (i.e. "secondary" SAM).

A select number of priority issues for which interventions are realistically available in resource-poor settings are highlighted below. Acute illnesses are not considered since they likely would be already identified and treated through existing initiatives such as the Integrated Management of Childhood Illness. A fuller review of clinical problems that underlie or contribute to infant <6m SAM in developing countries is needed in future.

i. Identification and treatment of HIV in infants <6m

Even though there are few explicit references to infants <6m as a special group, it is encouraging that most guidelines now refer to HIV in the context of SAM. The contribution of HIV to total disease burden of infant <6m SAM varies by setting but, even in low prevalence settings, the implications for affected individual patients are serious and, therefore, justify highlighting this issue.

Table 3

Risk–benefit summary table for HIV diagnosis and treatment in infants <6m

Existing recommendation/practice Many guidelines now refer to the treatment of HIV but none refer specifically to infants <6m.	
Proposed recommendation/practice (see also the NUGAG review on HIV) Guidelines should reference WHO 2010 guidelines for "HIV diagnosis and treatment in infants and children" (and any local guideline arising from this). The following key recommendations from the guidelines are of particular relevance to infants <6m: **Testing:** • "It is strongly recommended that all infants with unknown or uncertain HIV exposure being seen in health-care facilities…have their HIV exposure status ascertained. *[This will help to ensure that infants whose mothers were not tested during pregnancy* or delivery can still benefit from counselling and treatment to prevent breast-milk transmission. In addition, the identification of previously unrecognized exposed infants will also serve to identify women living with HIV, which, in turn, allows programmes to provide treatment and care to women, and prevent transmission of HIV during future pregnancies]".* *Or those whose mother was infected with HIV after a negative test in pregnancy. • "It is strongly recommended that all infants who are known to be exposed to HIV be tested at 4–6 weeks with virological assays to determine infection status. *[This will promote the early identification of infected infants and enable those children to access lifesaving treatment]".* **Treating:** • "It is strongly recommended to initiate ART in all HIV-infected infants diagnosed in the first year of life, irrespective of the CD4 count or whether the infant is sick. *[This recommendation has been in place since 2008 but has not been adequately implemented. The strength of the recommendation has been increased in light of recent findings that highlight the dramatic improvements in mortality seen when HIV- positive infants are initiated on treatment immediately at diagnosis]".*	
Quality of evidence (for outcomes deemed critical)	Strong The evidence for early infant diagnosis and treatment of HIV is strong.
Benefits/desired effects	To optimize both SAM and HIV outcomes, and to ensure efficiency of treatment programmes for both, it is critical to ensure that infant <6m SAM guidelines harmonize and link with other key guidelines for this age group. SAM treatment programmes are an important entry point to HIV treatment programmes (*24*) (both for an infant and the family) and there is good opportunity for synergy between the two.
Risks/undesired effects	To make a definitive diagnosis of HIV in infants <6m, virological testing is needed. This may not be universally available. Settings that rely on antibody tests alone risk false positive results in this age group.
Values/acceptability	While it is important to be mindful of any continuing stigma and sensitivity around HIV, it is more important to "normalize" the problem

	and ensure that all those needing treatment receive it. With strong evidence of benefit and increasingly widespread availability of ARV treatment, as well as guidelines for virologically (polymerase chain reaction/PCR) positive infants to immediately start ART regardless of CD4 or staging, it is now becoming unacceptable *NOT* to actively test for and treat HIV.
Costs	Resources are needed both for diagnosing and treating HIV.
Feasibility	A public health approach to HIV has proven successful in many settings. Linking existing HIV services to existing SAM services may increase the caseload for both but is important to ensure.
Final recommendation	In guidelines on infant <6m SAM, make explicit links with WHO 2010 guidelines on HIV.
Strength of recommendation	*Strong **OR** Conditional **OR** Qualified **OR** Weak* Strong
Quality of evidence that informs recommendation	*High/Moderate/Low/Very Low* High
Comments justifying recommendation	It is important because of the effect on survival of policies for immediate ART in infants who are confirmed to be HIV infected, regardless of CD4 percentage or clinical staging.
Gaps, research needs, comments	See above. Safety, efficacy and cost-effectiveness of any new assessment tool needs to be thoroughly tested.

ii. Identification and referral of chronic disease and disability

Table 4

Risk–benefit summary table for identifying and referring infants <6m with chronic disease or disability underlying SAM

Existing recommendation/practice Guidelines do not recognize chronic disease or disability as potentially underlying infant <6m SAM.	
Proposed recommendation/practice Guidelines should be explicit about the fact that chronic disease (e.g. congenital heart disease, some forms of which might be amenable to treatment, even in developing country settings) or disability might underlie or contribute to infant <6m SAM. Examples of conditions that could be identified and treated/referred in many developing country settings include: • TB: if there is a family history of TB or cough, referral to TB services should be made; • disability: nutrition service providers should be aware of and have a working relationship with: o clinicians who can make more definitive diagnoses (e.g. dysmorphic syndrome or early cerebral palsy where tone and swallowing may be abnormal); o relevant health service providers (e.g. physiotherapists for cerebral palsy; surgeons for treatment of cleft palate: an easily identified condition – though often only if looked for – whose prognosis is dramatically improved following treatment; surgery or even primary care for treatment of tongue-tie); o community and social organizations that can offer advice and often much needed social support to families with a disabled infant.	
Quality of evidence (for outcomes deemed critical)	Low While there is plentiful evidence regarding both TB (*25*) and disability (*26*), there is little specifically in the context of SAM.
Benefits/desired effects	A more holistic and integrated nutrition service. More holistic and integrated TB/disability/chronic disease services: with better links with local nutrition services these should also benefit, becoming better at preventing malnutrition and identifying/referring any that develop.
Risks/undesired effects	Sometimes there is social stigma and misunderstanding around TB, disability and any other chronic disease, thus screening and diagnosis should be sensitively managed to mitigate this. Unless follow-up services are available, the value and ethics of diagnosing chronic disease and disability could be questioned.
Values/acceptability	Depends on local context and availability of services.
Costs	Health service costs will increase with the greater workload of better-managed chronic disease and disability, however, there is a moral and ethical imperative not merely justifying but also demanding resource allocation to these vulnerable populations.
Feasibility	In many settings, front-line health workers have little formal training. Identifying and appropriately referring infants could be challenging, though simple algorithms could help.
Final recommendation	Ensure that chronic disease and disability (including minor problems such as tongue tie that potentially could interfere with breastfeeding) are recognized in new guidelines.
Strength of recommendation	*Strong* ***OR*** *Conditional* ***OR*** *Qualified* ***OR*** *Weak* Strong
Quality of evidence that	*High/Moderate/Low/Very Low*

informs recommendation	Very Low (in this context)
Comments justifying recommendation	Better linkages between different elements of health care and social support services should be promoted wherever possible: this update of infant <6m SAM guidelines represents one such key opportunity.
Gaps, research needs, comments	What is the prevalence of TB/disability/other chronic disease among infants <6m with SAM? How do they affect outcomes from SAM? If there is excess mortality with underlying conditions, how much is potentially avoidable and what can be done to reduce the avoidable mortality/morbidity?

iii. Catch-up with routine immunizations

Table 5

Risk–benefit summary table for recommending catch-up with routine immunizations as part of infant <6m SAM treatment

Existing recommendation/practice Some country guidelines recommend catch-up with any missed immunizations as a standard element of pre-discharge care.	
Proposed recommendation/practice International guidance on infants <6m to do the same.	
Quality of evidence (for outcomes deemed critical)	Strong Immunization programmes are based on strong evidence of mortality/morbidity benefit (*27*).
Benefits/desired effects	Ensure that no infants miss their routine immunizations. Infants with SAM are more vulnerable and could benefit more from full compliance with immunizations. Improving interprogramme linkages and communication (in this case between immunization and nutrition services) is always beneficial and in this case could lead to future opportunities (e.g. screening for infant <6m SAM at the time routine immunizations).
Risks/undesired effects	Best timing of immunization not clear.
Values/acceptability	Encouraging immunizations is likely to be widely accepted.
Costs	Time cost and some resource cost is added to nutrition programmes to ensure that this part of the guideline is completed.
Feasibility	Given widespread availability of routine immunizations in most settings, implementing this is unlikely to present any significant problems.
Final recommendation	As proposed.
Strength of recommendation	*Strong* ***OR*** *Conditional* ***OR*** *Qualified* ***OR*** *Weak* Strong
Quality of evidence that informs recommendation	*High/Moderate/Low/Very Low* Moderate (since no direct evidence that it makes a difference to outcome of infant <6m SAM)
Gaps, research needs, comments	Quantify the prevalence of incomplete immunizations among infants <6m. Check seroconversion rates following immunizations. Explore the potential for immunization services to screen for infant. <6m SAM at same time as routine vaccinations.

5.2.3 Social/carer-focused interventions for infant <6m SAM

Again, many issues could come under this section: some worthy of their own review; some worthy of noting without the need for a formal review (e.g. the need to consider and treat illness in carers as well as infants – notably if issues such as TB or HIV are identified).

Only two key interventions are highlighted here.

i. Nutritional supplementation and fluid intake for breastfeeding carer

Table 6

Risk–benefit summary table for optimizing nutritional supplementation and fluid intake for breastfeeding carers of infant <6m SAM

Existing recommendation/practice Most current guidelines recommend that a breastfeeding carer: • drinks at least 2 litres of water per day • eats a diet of 2500 kcal/day (not always clear whether a programme is expected to supply this or whether mothers merely educated on this need for increased intake).	
Proposed recommendation/practice In line with the WHO 2009 model chapter on "Infant and Young Child Feeding" (IYCF), recommend that a mother's intake increases by 10% if she is not active; by 20% if she is moderately or very active (assume the latter in cases of infant <6m SAM). Recommend plentiful fluid intake for lactating mothers.	
Quality of evidence (for outcomes deemed critical)	Low Guidelines on nutrition for breastfeeding mothers are well established. While it is plausible and likely that closer adherence will improve outcomes from infant <6m SAM, evidence of effectiveness is needed.
Benefits/desired effects	Increased probability of successful EBF. Mothers feel more supported and hence more empowered to care for their infants.
Risks/undesired effects	Cost-effectiveness potentially limited (especially if carer rations are shared with others once the infant goes home).
Values/acceptability	Likely to be popular and well accepted by carers. Normative organizations such as WHO and also programme funders may want stronger direct evidence for effectiveness in this patient group before substantial investment.
Costs	Providing a full (or top-up) diet for mothers likely to be costly.
Feasibility	Very simple to deliver in most settings – breastfeeding mothers already supported in some settings.
Final recommendation	Support adequate nutrition and fluid intake for breastfeeding mothers and link with WHO IYCF guidelines to facilitate this.
Strength of recommendation	*Strong* ***OR*** *Conditional* ***OR*** *Qualified* ***OR*** *Weak* Strong
Quality of evidence that informs recommendation	*High/Moderate/Low/Very Low* Low
Comments justifying recommendation	Inserting this recommendation would facilitate closer links with WHO guidelines on IYCF.
Gaps, research needs,	How best to deliver the additional nutritional needs of pregnancy (e.g.

comments	health education to encourage better home diet; cash transfer for the same; ready-to-use supplementary food). Effectiveness of dietary interventions aimed at mother on infant outcomes.

ii. Psychosocial interventions for mother/carer of infant <6m

Table 7

Risk–benefit summary table for supporting carer mental health (psychosocial support)

Existing recommendation/practice Most current guidelines recommend that the carer be "supported" and "reassured" and that staff should be "attentive" and explain all aspects of treatment. Some guidelines recommend special care is needed for depressed and traumatized mothers.	
Proposed recommendation/practice Highlight psychosocial support for carers as part of the treatment package for infant <6m SAM. Make links with local mental health and psychosocial support programmes wherever available (e.g. following example chapters in WHO 2006 "Integrated management of pregnancy and childbirth").	
Quality of evidence (for outcomes deemed critical)	Moderate Reviews have highlighted the link between maternal mental health and infant growth (*28*). There are plausible mechanisms whereby this association could be causal. There is some work highlighting the importance of psychosocial issues in infant <6m SAM (*4*,*29*).
Benefits/desired effects	Better support of mothers/carers (an important objective in itself). By better supporting mothers and carers, better infant outcomes.
Risks/undesired effects	Negligible
Values/acceptability	Strategies offering psychosocial support need to be culturally sensitive and understand local ways in which carers express and present with mental health issues.
Costs	Emphasizing positive staff attitude to carers and encouraging greater sensitivity/understanding around mental health issues costs nothing. More formal psychosocial interventions need trained staff and separate programmes – these mainly need staff and facility costs.
Feasibility	There should be no major obstacles to increasing general awareness of mental health issues among nutrition programme staff. Availability of effective mental health/psychosocial services likely to vary greatly in different settings.
Final recommendation	As described
Strength of recommendation	*Strong* ***OR*** *Conditional* ***OR*** *Qualified* ***OR*** *Weak* Strong (reasonable potential for benefit against negligible risk)
Quality of evidence that informs recommendation	*High/Moderate/Low/Very Low* Moderate
Comments justifying recommendation	Separate review of mental health/psychosocial issues could further support this recommendation.
Gaps, research needs, comments	What is the prevalence of mental health problems among carers of infant <6m with SAM? What interventions can better support both carers and infants?

5.3 Risk–benefit summary tables for nutritional interventions for infant <6m SAM

- ***Division of infants <6m into "those who can" and "those who cannot" breastfeed***

Table 8

Risk–benefit summary table for dividing infants <6m into two groups: those who can and those who cannot breastfeed

Existing recommendation/practice Most country guidelines on infant <6m SAM divide infants <6m into two groups: those who can and those who cannot breastfeed.	
Proposed recommendation/practice International guidance on infants <6m to do the same. Reference WHO 2009 guidelines (or local equivalent) for "Acceptable medical reasons for use of breast milk substitutes" (*30*) (though note that this does not yet reference WHO 2010 guidelines for "HIV diagnosis and treatment in infants and children" – this would need to be highlighted to avoid confusion).	
Quality of evidence (for outcomes deemed critical)	Low There is no direct evidence on this issue, including on prevalence of the two conditions.
Benefits/desired effects	Recognizes the real-world challenges around managing orphans. Treatment is appropriately targeted and planners can more easily take into account needs of non-breastfed infants. Harmonizes with other WHO guidance on medical reasons why an infant may need BMS (e.g. severe maternal illness) (*30*).
Risks/undesired effects	There is a potential for supplier-induced demand whereby infants who could potentially be breastfed (e.g. wet-nursed by a female relative) opt for or end up in the "non-breastfed" group due to availability of that treatment. Recommendations for individual care (that BMS is sometimes needed) may get confused with public health messages to EBF for 6–12 month olds.
Values/acceptability	This recommendation is unlikely to be challenged
Costs	Long-term BMS until 6–12 months old is expensive. Formal recognition of infants <6m who cannot be breastfed may lead to difficult questions around whether governments, NGOs and other service providers should provide for longer term as well as immediate BMS needs.
Feasibility	In the short term, there is no problem with this recommendation. The challenges of longer term BMS (whoever the provider) should be carefully considered at the country level before emphasizing short-term treatments for infants who cannot be breastfed.
Final recommendation	As proposed
Strength of recommendation	*Strong* ***OR*** *Conditional* ***OR*** *Qualified* ***OR*** *Weak* Strong
Quality of evidence that informs recommendation	*High/Moderate/Low/Very Low* Low
Gaps, research needs, comments	Quantify the prevalence of the two groups of infants <6m. Formal and operational research to explore what % of "infants who cannot breastfeed" are due to avoidable factors. Further research on

♦ *Potential renal solute load (PRSL) and choice of therapeutic milk*

PRSL was discussed in depth at the 2004 WHO consultation on SAM:

- lower values are preferable because a malnourished infant has reduced ability to concentrate urine and is at risk of negative water balance, hypernatraemic dehydration;
- the maximum value for well nourished children was cited as 223 mOsmol/l;
- it also was noted that the actual renal solute load might be lower in severely malnourished children due to rapid tissue deposition – thus the safety of F-100 for infants who are rapidly gaining weight is unclear.

Estimates of PRSL were tabulated at the consultation as:

human milk	93	mOsmol/l
milk-based formulas	135–177	mOsmol/l
F-75	154	mOsmol/l
F-100	360	mOsmol/l
F-100d	238	mOsmol/l

The WHO consultation broadly agreed the following:

- Stabilization phase: Until definitive data are forthcoming, the guidelines set out for stabilization with F-75 should be followed for infants <6. Diluted F-100 was considered inappropriate because its PRSL is marginal and its higher protein, sodium and lactose content is disadvantageous. Where available, expressed breast milk was seen as a possible alternative to F-75.
- Rehabilitation phase: The actual renal solute load is related to the rate of weight gain. The PRSL is high for F-100 and some members of the consultation felt it should not be used as it exceeds the upper limit recommended by the Life Sciences Research Office. Some felt that F-100 should not be used for infants <4 months. Expressed breast milk, infant formula or diluted F-100 were seen as possible alternatives. Others considered that F-100 might be appropriate if weight gain is rapid.

♦ *Optimal feeding of low-birth-weight (LBW) infants in low- and middle-income countries*

Where an infant is LBW (<2500 g at birth), recently updated WHO 2010 guidelines should be referred to. Since birth weight is very often unknown in settings where SAM is present, and since LBW may be overrepresented in SAM populations (*31*), the following weak recommendations for supplementing very LBW infants might also be considered for SAM infants <6m:

- vitamin D 400–1000 IU/day until six months;
- if breastfed, give extra calcium at 120–140 mg/kg/day, phosphorous 60–90 mg/kg/day;
- 2–4 mg/kg/day iron starting at two weeks and continuing until six months.

♦ *Infant age*

Infant physiology changes rapidly over the first 6 months of life. Current guidelines rarely recognize this but future ones should. A 0–2 month old is very different from a 2–4 month old who in turn is different from a 4–6 month old. This can sometimes alter risk–benefit balances of treatment.

5.3.1 What is the safest and most effective therapeutic feeding strategy during stabilization phase treatment (which milk at what volume)?

Table 9

Risk–benefit summary table for feeding strategy during stabilization (which milk at what volume)

Existing recommendation/practice Most country guidelines recommend feeds every three hours (30–60 minutes after a breastfeed if infant is still being breastfed). Most country guidelines recommend 100 kcal/kg/day of feeds (approximately 130 ml/kg/day of F-100d). Guidelines on which milk to use vary: Most country guidelines recommend F-100d → *Half of those recommend that F-75 be used in place of F-100d in oedematous SAM.* The 2004 WHO consultation proposed that only F-75 was suitable, cautioning against undiluted F-100 due to concerns about potentially high PRSL.	
Proposed recommendation/practice Recommend three hourly feeds (with preceding breastfeed if infant is still being breastfed). Recommend 100 kcal/kg/day feeds. *Several options are available regarding which milk:* **Option 1** F-100d for all **Option 2** F-100d but F-75 for oedematous SAM **Option 3** F-75 for all **Option 4** Formula for all	
Quality of evidence (for outcomes deemed critical)	Low There is sparse direct evidence for any of these options.
Benefits/desired effects (of the complicated/uncomplicated approach to infant SAM)	**Option 1** F-100d for all Simplicity. **Option 2** F-100d but F-75 for oedema Avoids high PRSL in situation where fluid balance most precarious. **Option 3** F-75 for all Simplicity; availability; formulated for SAM; low PRSL. **Option 4** Formula for all Simplicity and clarity, especially for those who cannot be breastfed; can involve mother from the beginning and educate her to make up the formula safely; formula available in most settings even if formal F-75/F-100 supply lines interrupted.
Risks/undesired effects	**Option 1** F-100d for all PRSL potentially too high. Future availability could be limited with more use of RUTF in place of traditional transition F-100. Add to kitchen workload – with F-75/F-100/F-100d all being made,

	mistakes are more likely in making up the feed correctly. **Option 2** F-100d but F-75 for oedema Same as option 1, but adds extra complexity to the protocol. **Option 3** F-75 for all PRSL still higher than formula or breast milk; even though formulated for SAM, formulation based mostly on expert opinion and physiological reasoning rather than RCT-type evidence. **Option 4** Formula for all Not formulated for SAM and could cause confusion regarding which formula to use. Risks sending out an unintended message to carers and the wider population that formula milk is a "cure" for SAM – could undermine EBF. Option for lactose-free formula to be used.
Values/acceptability	**Options 1–3** All likely to be equally acceptable to carers and centre staff. **Option 4** Relationship with formula manufacturers around supplies of formula need to be carefully managed and would need to follow codes of practice around BMS.
Costs	**Options 1–3** Minimal differences in cost between these options. **Options 1 and 2** Making up separate F-100d more costly in terms of staff time. **Option 4** Potentially the cheapest option given widespread availability.
Feasibility	**Options 1–3** Supply lines already exist in most settings for pre-packaged milks; can also be made locally if needed (recipes already widely available). **Options 1–2** Adds potentially unnecessary complexity making up a new feed. **Option 4** Simplicity and clarity, especially for those who cannot be breastfed; can involve mother from the beginning, supporting centre staff. New ready-to-use formulas packaged in cartons could also make this an attractive short-term option in emergencies where water supplies are especially poor.
Final recommendation	Feed frequency, amount – three hourly feeds at 100 kcal/kg/day. Milk type – Option 4 (infant formula – consider lactose free if possible).
Strength of recommendation	*Strong **OR** Conditional **OR** Qualified **OR** Weak* Conditional (on availability of different feeds in different settings)
Quality of evidence that informs recommendation	*High/Moderate/Low/Very Low* Low
Comments justifying recommendation	Option 4 is recommended on grounds of simplicity and trying to engage non-breastfed mothers as much as possible as early as possible.
Gaps, research needs, comments	More RCTs comparing different types of formula against F-75/F-100. Use of specialized formula milks such as lactose-free formula. Physiological measurements (e.g. bloods/urine osmolality) to provide in-depth information on different feed formulations. Qualitative work to ensure correct "messages" go out to the community to avoid any inadvertent undermining of EBF messaging.

5.3.2 What is the safest and most effective therapeutic feeding strategy during transition and rehabilitation phase treatment (which milk at what volume)?

Table 10

Risk–benefit summary of feeding strategy during transition and rehabilitation

Existing recommendation/practice For breastfed infants: Most country guidelines recommend: stepping down the volume of BMS (most often F-100d) as breast milk is re-established and adequate weight gain is achieved (20 g/day); stopping BMS altogether once weight gain adequate and (after five days further observation) discharging home with follow-up (details vary). For infants with no possibility to breastfeed: Most country guidelines recommend increasing the BMS (most commonly F-100d) to 150–200 kcal/kg/day once infant is stable; discharge home on formula milk once cure criteria (see admission/discharge criteria review) achieved and infant clinically stable.	
Proposed recommendation/practice International guidance on infants <6m to outline general principles of transition/rehabilitation: BMS step-down (in case of breastfed) and step-up of BMS with eventual switch to formula (in case of non-breastfed infants). **Option 1** International guidelines to outline principles *and* specify details of transition/rehabilitation **Option 2** International guidelines to outline principles but *not* details of transition/rehabilitation	
Quality of evidence (for outcomes deemed critical)	Low There is no direct evidence on details of transition or rehabilitation.
Benefits/desired effects	**Option 1** (principles *and* details) Standardizes and offers clearer guidance to developers of new protocols. **Option 2** (principles but *not* details). Leaves more scope for local adaption and research.
Risks/undesired effects	**Option 1** (principles *and* details) Any guidelines would not be based on high quality evidence. **Option 2** (principles but *not* details) Programmes could adopt dangerous or inappropriate options rather than ones about which there is genuine equipoise.
Values/acceptability	Depends on audience.
Costs	Depends on which option chosen; any options leading to longer rather than shorter patient say would increase treatment costs.
Feasibility	–
Final recommendation	**Option 2** (principles but *not* details)
Strength of recommendation	*Strong **OR** Conditional **OR** Qualified **OR** Weak* Conditional (depends on context how much detail is needed)
Quality of evidence that informs recommendation	*High/Moderate/Low/Very Low* Low
Gaps, research needs, comments	Which formula is best for non-breastfeeding infants and for how long? Are other nutritional supplements (vitamin D, calcium, phosphorous, iron needed (see section 5.3c)?

5.3.3 What is the safest and most effective therapeutic feeding protocol (time in stabilization phase, time in transition, criteria for phase progression)?

Table 11

Risk–benefit summary of feeding protocols (time in each phase, criteria for progression)

Existing recommendation/practice See table 10. Many similarities, but varied details, about how long to spend in each phase of treatment and how quickly to progress.	

Proposed recommendation/practice
Option 1
International guidelines to outline general principles *and* specify suggested details of transition/rehabilitation.
Option 2
International guidelines to outline principles but *not* details of transition/rehabilitation
Principles to highlight include:
• balancing risks and benefits (which will be very context specific) of:
  ○ longer hospital stay that may improve outcomes through closer supervision and being able to directly and quickly address problems *but* has the downside of opportunity cost to carers, cost of health-care systems and more nosocomial infection;
  ○ short hospital stay – opposite risks;
• simplicity:
  ○ in general, simple guidelines are to be preferred over more complex ones since they are more likely to be effective in routine practice in most settings.	

Quality of evidence (for outcomes deemed critical)	Low There is no direct evidence on details of feeding protocol.
Benefits/desired effects	**Option 1** (principles *and* details) Standardizes, offers clearer guidance to developers of new protocols. **Option 2** (principles but *not* details) Leaves more scope for local adaption and research.
Risks/undesired effects	**Option 1** (principles *and* details) Any guidelines would not be based on high quality evidence. **Option 2** (principles but *not* details) Programmes could adopt dangerous or inappropriate options rather than ones about which there is genuine equipoise.
Values/acceptability	Depends on audience.
Costs	Depends on which option chosen; any options leading to longer rather than shorter patient stay would increase treatment costs.
Feasibility	–
Final recommendation	**Option 2** (principles but *not* details)
Strength of recommendation	*Strong **OR** Conditional **OR** Qualified **OR** Weak* Conditional – depends on context how much detail is needed
Quality of evidence that informs recommendation	*High/Moderate/Low/Very Low* Low
Gaps, research needs, comments	The difficult balance between too short and too long patient stay would not be as relevant were community-based options available to more patients.

5.3.4 What is the most effective mode of therapeutic feeding (SS or cup feeding or spoon feeding)?

Table 12

Risk–benefit summary of most effective mode of therapeutic feeding

Existing recommendation/practice For infants with the potential to breastfeed, almost all guidelines recommend relactation via SS (also called supplemental suckling) as the main mode of therapeutic feeding. Restoring effective EBF is the main aim of treatment.Since restoring EBF is the main aim of treatment, cup feeding and spoon feeding are rarely mentioned.	
Proposed recommendation/practice International guidance to also recommend restoration of EBF as a major treatment aim. For inpatients, this is to be done using SS (for relactation/increased lactation). Cup feeding or spoon feeding can be recommended for infants with no possibility of breastfeeding.	
Quality of evidence (for outcomes deemed critical)	Low Though there are many observational studies in other settings and other patient groups, evidence for SS in infants <6m SAM is scant.
Benefits/desired effects	Restore effective EBF. Programmes make it clear that their main goal is to support EBF. Promoting cup feeding and spoon feeding for non-breastfeeding infants much lower risk than bottle feeding in terms of infection risk.
Risks/undesired effects	For infants with uncomplicated SAM where EBF has not completely stopped, breastfeeding support may be equally effective yet have lower risks since admission not needed/BMS not needed. Does not address the root problem of *why* breastfeeding stopped or became ineffective – there is potential for relapse unless this is done.
Values/acceptability	Evidence from the MAMI project show split opinions on SS: some programmes find it works very well; others find it does not work or is too resource intensive for their setting. One interpretation of this mixed experience is that efficacy may be good but effectiveness low; it requires significant "inertia" to get established within a treatment programme.
Costs	Inpatient admission for SS overall costly (both for the health system and for the carer).
Feasibility	Even if SS could be made more effective and easier to implement (e.g. better training tools), it is unlikely there is enough treatment capacity within many health-care/nutrition settings to offer SS to all who need it.
Final recommendation	As noted
Strength of recommendation	*Strong* ***OR*** *Conditional* ***OR*** *Qualified* ***OR*** *Weak* Qualified Can be strongly recommended for complicated inpatients but note serious issues regarding coverage and risk–benefit ratio for those still breastfeeding and who might equally have benefited from more general breastfeeding support.
Quality of evidence that informs recommendation	*High/Moderate/Low/Very Low* Low
Gaps, research needs, comments	How to improve effectiveness/ease of use of SS. Better patient selection for SS vs more general breastfeeding support (e.g. positioning advice).

5.4 Conclusions

5.4.1 The evidence base for treating infant <6m SAM is limited and weak

The main finding of this review is that evidence on the treatment of infant <6m SAM is both limited and weak. This echoes findings from the accompanying review on admission/discharge criteria for infant <6m SAM (*8*). It is also consistent with the 2010 MAMI project, which highlighted the problem of infant <6m SAM being overlooked (*4*).

5.4.2 Paucity of evidence has not hindered important country-level advances in guidance on infant <6m SAM

Relevant to the WHO guideline update process, another key finding is that most SAM-affected countries are already very actively engaged with infant <6m SAM. At least as is reflected in national policies on SAM: what happens at the front-line field level is of course a different issue. Things have moved on considerably since the one lone mention of this group in the WHO 1999 guidelines for "Treatment of severely malnourished children" (*32*).

Where sections of national SAM guidelines are devoted to infants <6m, these have many strengths as assessed by the AGREE tool (clarity of scope and purpose; engagement with professional stakeholders; clarity of presentation; provision of support materials). Their major weakness is that they are not based on explicit high-quality evidence.

5.4.3 Current country-level approaches to infant <6m SAM are out of step with current approaches to management in the older child

Current guidance on infant <6m SAM is inconsistent with key principles underpinning current treatments for older children. There is:

- No separation of complicated and uncomplicated infant <6m SAM

  While infants are physiologically more vulnerable than older children and while pathologies underlying infant <6m SAM are likely more common and more complex/wide ranging, it is difficult to believe that there is not a group of infants <6m who have anthropometrically-defined SAM, but are clinically stable. Indeed, as WHO-GS replace NCHS growth references, there will suddenly be three million "more" infants who fall below the WHZ -3 threshold (*33*). Previously, these would not have been eligible (unless there were other problems) for any specific treatment. It is implausible that they all, without exception, now need admission as per current guidelines.

- No outpatient-based/public health-orientated model of care

  Having inpatient care alone greatly limits treatment capacity and consequent public health impact of any treatment programmes. As realized more than 10 years ago for the treatment of SAM in older children, adequate population coverage and easy access to care are key. It is these that optimize public health impact, and it is these that are only realistically achieved if outpatient-based, low-opportunity-cost models of care are

developed to complement (rather than replace) resource and time-intensive inpatient treatments (*21*,*34*,*35*).

5.4.4 Future guidance should be better at recognizing and addressing clinical, psychological, social and other non-nutritional determinants of infant <6m SAM

National guidelines on infant <6m SAM focus heavily on improving the quality and quantity of nutritional intake. While this is appropriate to short-term needs, it is helpful to recognize that a wide range of factors may underlie or contribute to infant <6m SAM. Even if breastfeeding failure (implicitly the one major problem according to all current guidelines) is the immediate cause of SAM, it is critical to ask "*why* did this occur". Unless "upstream" problems are actively considered and addressed, recurrence is likely once the infant returns to the home setting. Similarly, unless the many medical problems that cause SAM are actively considered during assessment and treatment, there is a danger that they may be forgotten or ignored. By encouraging better links and integration with other health (e.g. HIV, TB, disability) and social programmes (e.g. psychosocial support for carers), there is great scope for synergy and great potential to improve key outcomes from them all. Fuller review of these issues and potential interventions is needed in future.

5.4.5 Weak evidence should not hinder important advances in international guidance on infant <6m SAM

Paucity of evidence to make *strong* recommendations does not mean – and clearly has not meant – that *no* recommendations can be made. The care of children aged 6–59 months underwent a radical shift from a highly medicalized inpatient-only model of care to a public health, community-focused system without high-quality RCT evidence supporting the move. With regard to infants <6m:

- Current guidelines cannot be viewed as "Gold Standard" because they are not based on gold standard evidence.

  The positive aspect of this is that it creates the equipoise needed to underpin future intervention research. It also highlights the need for future research focused on this age group, especially that aimed at harmonizing infant <6m SAM with child SAM approaches.

- Even just acknowledging infant <6m SAM in revised WHO 2012 guidelines would be a significant step forward.

  It would help:

  - stimulate both formal and informal (operational) research on this group;
  - support and better engage with what is already happening at the country level;
  - better integrate SAM guidance materials to other global initiatives, such as Scaling Up Nutrition (SUN), which recognize the importance of intervention throughout the life-course and especially emphasize early life (*36*).

5.4.6 Clinically useful guidance on nutritional treatments for infant <6m SAM is possible

Several key messages regarding nutritional treatment of infant <6m SAM emerge from this review.

Overall:

- Infants <6m should be divided into two groups: those who have the potential to breastfeed (the goal being restoration of effective EBF) and those who do not (evidence LOW; recommendation STRONG).

- Infants who are LBW should follow the WHO 2010 guidelines for this group. Since birth weight is often unknown, recommendations, which could potentially apply to SAM infants <6m of unknown birth weight, include supplementing with vitamin D, calcium, phosphorous and iron (evidence LOW; recommendation WEAK).

- An infant's age should be considered much more than it is now – it affects both the prognosis and risk–benefit balance of various therapeutic options (e.g. a young infant who has only recently stopped EBF is much more likely to resume successfully and will benefit more than an older 5–12 month infant who stopped age 1 month) (evidence LOW; recommendation STRONG).

What is the safest and most effective feeding strategy during the stabilization phase?

- There are several potential options. Infant formula milk at 100 kcal/kg/day might have the best balance of risks and benefits. The major advantage is simplicity, especially over more complex options such as F-100d. Formula is nearest in composition to breast milk and has lower PRSL than other milks. It also creates opportunities for specialist formulations such as low-lactose formulas (evidence LOW; recommendation CONDITIONAL – on availability of different feeds in different settings).

What is the safest and most effective strategy during the transition and rehabilitation phase?

- Again, there are several possible options. For non-breastfed infants, BMS (formula or F-100) should be stepped up; for breastfed infants it should be stepped down as breast milk is re-established. International guidance should specify principles rather than details (evidence LOW; recommendation CONDITIONAL - depends on context how much detail is needed).

What is the safest and most effective therapeutic feeding protocol?

- Basic principles of increasing feed volume for non-breastfed infants and re-establishing breastfeeding wherever possible are relatively clear. Exact details of how this should be done are not clear and should be left to local discretion (evidence LOW; recommendation CONDITIONAL – level of detail depends on context).

What is the safest and most effective mode of delivery of therapeutic feeds?

- For inpatients who have the possibility to restore EBF, therapeutic feeds can best be delivered by SS (evidence LOW; recommendation QUALIFIED – note issues regarding population coverage with this approach and risk–benefit differences in infants who are still breastfeeding, with less complicated SAM).

5.4.7 Now is the right time to tackle infant <6m SAM

There are several reasons why infants <6m should play a much more prominent role in future health and nutrition programming:

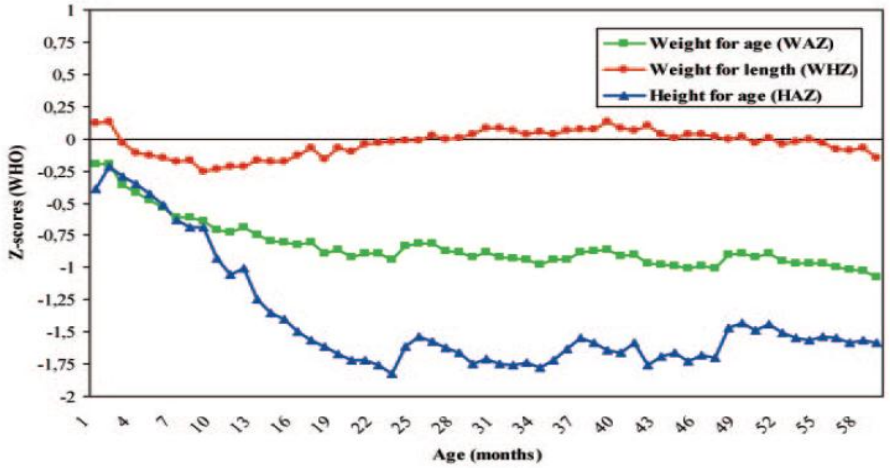
- Increasing evidence on shortand long-term impact of early life nutrition

  There is increasing scientific recognition of the role of early life nutrition on long-term health outcomes (*37*,*38*). With chronic disease becoming more prevalent even in developing countries, tackling infant <6m SAM could have long-term as well as short-term benefits.

- Early onset of malnutrition

  A recent analysis of child growth patterns in 54 developing countries found that mean weight began to falter at about 3 months (Figure 2) (*39*). The authors concluded that "these findings highlight the need for prenatal and early life interventions to prevent growth failure". As obvious from the main study results, waiting until 6 months to focus on SAM represents important opportunities lost.

Figure 2 **Mean anthropometric z-scores by age, in 54 studies, relative to WHO-GS**



Source: Victora et al. (*39*).

- Right timing and political will to tackle early life malnutrition

  As well as persuasive scientific reasons to tackle infant <6m SAM, now is a particularly good time politically to support this group. SUN is a major international movement involving the United Nations (UN), multilateral and bilateral development agencies, foundations, developing countries, NGOs and other civil society organizations, researchers and the private sector that aims to "sharply scale up evidence-based, cost-effective interventions to prevent and treat undernutrition, with highest priority to the minus 9 to 24-month window of opportunity where we get the highest returns from investments".

In conclusion, there has never been as good a time as now to refocus on and highlight SAM in infants <6m.

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