

Revising WHO guidelines on the management of children with severe malnutrition

*Commonwealth Association for Paediatric Gastroenterology and Nutrition
London, 21-23 July 2011*





Revising WHO guidelines on the management of children with severe malnutrition

*Commonwealth Association for Paediatric Gastroenterology and Nutrition
21-23 July 2011, London*

Metabolic changes while reversing reductive adaptation

Physiological change	Malnourished (M)	Recovered (R)	$\frac{M-R}{R}$ (%)
Metabolic rate, kJ/kg ^{0.75} /day	315	417	-24
Sodium pump activity, turnover of pool per hour	3.62	4.94	-27
Intracellular sodium, mmol/kg DS ^a	169	109	+55
Intracellular potassium, mmol/kg DS ^a	341	387	-12
Protein synthesis, g/kg/day	4.0	6.3	-37
Protein breakdown, g/kg/day	3.7	6.4	-42
Cardiac output, l/min/m ³	4.77	6.90	-31
Stroke volume, ml/beat/m ³	44.1	53.0	-22
Circulation time, seconds	13.7	10.5	+30
Glomerular filtration rate, ml/min/m ³	47.1	92.4	-41
Renal blood flow, ml/min/m ³	249	321	-22
H ⁺ excretion after NH ₄ Cl, μ equiv/min	10.4	28.4	-63
Osmolal clearance rate, ml/min	0.20	0.66	-70
Sodium excreted, % of infused	22.3	48.7	-54
Sodium excreted, % of sodium filtered			
normal ECF	0.50	1.23	-59
expanded ECF	0.82	11.07	-93
Response to temperature change	poikilotherm	homoeotherm	

Scientific paradigms

- Protein paradigm 1930-1970
- Energy paradigm 1970
- Hospital for case-management 1970-2005
- Free radical paradigm 1987
- Micronutrient paradigm 1990

1999.....

Management of severe malnutrition: a manual for physicians and other senior health workers



World Health Organization
Geneva

MANAGEMENT OF THE CHILD WITH A SERIOUS INFECTION OR SEVERE MALNUTRITION

Guidelines for care at the first referral level in developing countries





 DEPARTMENT OF CHILD AND ADOLESCENT SURVIVAL
 WORLD HEALTH ORGANIZATION

CHAPTER 7 Severe malnutrition

Severe malnutrition is defined in these guidelines as the presence of oedema of both feet, or severe wasting (<70% weight-for-height or <-3SD^a), or clinical signs of severe malnutrition. No distinction has been made between the clinical conditions of kwashiorkor, marasmus, and marasmic kwashiorkor because the approach to their treatment is similar.

Children with severe malnutrition are at risk of several life-threatening problems like hypoglycaemia, hypothermia, serious infection, and severe electrolyte disturbances. Because of this vulnerability, they need careful assessment, special treatment and management, with regular feeding and monitoring. Their treatment in hospital should be well organized and given by specially trained staff. As recovery may take several weeks, their discharge from hospital should be carefully planned in order to provide outpatient care to complete their rehabilitation and to prevent relapse.



Child with kwashiorkor

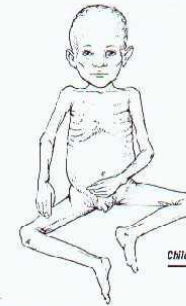
Diagnosis

Key diagnostic features are:

- weight-for-length (or height) <70% or <-3SD^a (marasmus)
- oedema of both feet (kwashiorkor or marasmic kwashiorkor).

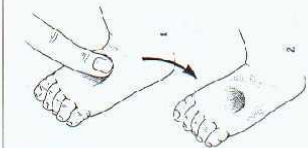
Note:

If weight-for-height or weight for length cannot be measured, use the clinical signs for marasmus or visible severe wasting (see Figure on the left). A child with visible severe wasting appears very thin and has no fat. There is severe wasting of the shoulders, arms, buttocks and thighs, with visible rib outlines.



Child with marasmus

^a SD = standard deviation score or Z-score. A weight-for-height of <-2SD indicates the child is at the lower end of the normal range, and <-3SD indicates severe wasting. A weight-for-height of <-3SD is approximately equivalent to 70% of the weight-for-height of the average (median) child (see chart on pages 147-148).



Pitting oedema on dorsum of foot. After applying pressure for a few seconds, a pit remains after the finger is removed.



COMMUNITY-BASED MANAGEMENT OF SEVERE ACUTE MALNUTRITION

A Joint Statement by the World Health Organization, the World Food Programme, the United Nations System Standing Committee on Nutrition and the United Nations Children's Fund

Why is the management of severe malnutrition not visible in the international health agenda?

How many child deaths can we prevent this year?

Lancet 2003; 362: 13.

	Estimated under-5 deaths prevented	
	Number of deaths ($\times 10^3$)	Proportion of all deaths
Preventive interventions		
Breastfeeding	1301	13%
Insecticide-treated materials	691	7%
Complementary feeding	587	6%
Zinc	459 (351)*	5% (4%)*
Clean delivery	411	4%
Hib vaccine	403	4%
Water, sanitation, hygiene	326	3%
Antenatal steroids	264	3%
Newborn temperature management	227 (0)*	2% (0%)*
Vitamin A	225 (176)*	2% (2%)*
Tetanus toxoid	161	2%
Nevirapine and replacement feeding	150	2%
Antibiotics for premature rupture of membranes	133 (0)*	1% (0%)*
Measles vaccine	103	1%
Antimalarial intermittent preventive treatment in pregnancy	22	<1%
Treatment interventions		
Oral rehydration therapy	1477	15%
Antibiotics for sepsis	583	6%
Antibiotics for pneumonia	577	6%
Antimalarials	467	5%
Zinc	394	4%
Newborn resuscitation	359 (0)*	4% (0%)*
Antibiotics for dysentery	310	3%
Vitamin A	8	<1%

The GRADE approach

Grading of Recommendation Assessment, Development and Evaluation

www.GradeWorking-Group.org

- Since 2007, WHO's process of producing guidelines have changed
 - The GRADE approach is a key component of this process.
- The aim is to ensure that WHO guidelines are consistent with internationally accepted best practices, including the appropriate use of evidence.

Developing recommendations: eminence and evidence

- Judgments about evidence and recommendations in healthcare are complex and need to consider issues such as feasibility and cost in addition to clinical efficacy
- Steps include
 - Framing the appropriate questions and deciding the relevant outcomes
 - Identifying evidence to address these questions
 - Assessing the quality of that evidence
 - Determining if a specific method does more good than harm compared with other existing methods

GRADE Process

Evidence retrieval
Assessment of its quality

```
graph TD; A[Evidence retrieval  
Assessment of its quality] --> B[Risk/benefit analysis  
Acceptability  
cost and feasibility]; B --> C[Recommendation];
```

Risk/benefit analysis
Acceptability
cost and feasibility

Recommendation

The **G**rading of **R**ecommendations **A**ssessment, **D**evelopment and **E**valuation

www.gradeworkinggroup.org/

Preparation and evidence retrieval



The GRADE evidence profile

Quality assessment						Summary of findings					
						No of patients		Effect			Quality
No of studies (Ref)	Design	Limitations	Consistency	Directness	Other considerations	Intervention	Control	Baseline risk (without treatment) (95%CI)	Relative risk (95%CI)	NNT/NNH (95%CI)	
Benefits:											
Outcome											
Harms:											
Outcome											
Footnotes:											

Examples from the IOL Guidelines

1.1. IOL AT TERM AND BEYOND

Table: 1.1.1

Question: (A) Labour induction versus expectant management by gestational age (all trials) for improving birth outcomes for women at or beyond term

Bibliography: Gülmezoglu AM, Crowther CA, Middleton P. Induction of labour for improving birth outcomes for women at or beyond term. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							(A) Labour induction versus expectant management by gestational age (all trials)	control	Relative (95% CI)	Absolute		
A2 Caesarean section												
20	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	697/3544 (19.7%)	774/3529 (21.9%) 15%	RR 0.92 (0.8 to 1.06)	18 fewer per 1000 (from 44 fewer to 13 more) 12 fewer per 1000 (from 30 fewer to 9 more)	⊕⊕⊕⊕ MODERATE	CRITICAL
A4 Apgar score less than 7 at 5 minutes - 41 completed												
6	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	INCONSISTENCY	0	No severe heterogeneity ($I^2 < 60\%$ or $Chi^2 \geq 0.05$)			
								-1	Severe, non-explained, heterogeneity ($I^2 \geq 60\%$ or $Chi^2 < 0.05$) If heterogeneity could be caused by publication bias or imprecision due to small studies, downgrade only for publication bias or imprecision (i.e. the same weakness shouldn't be downgraded twice)			
A4 Apgar score less than 7 at 5 minutes - 42 completed												
4	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	INDIRECTNESS	0	No indirectness			
								-1	Presence of indirect comparison, population, intervention, comparator, or outcome.			

GRADE – 4 levels of evidence

The extent to which one can be confident that an estimate of the effect or association is correct.

High	Further research unlikely to change the evidence
Moderate	Further research likely to have impact on the evidence
Low	Further research is very likely to have an impact on the evidence
Very low	Estimate of quality is very uncertain

Strength of recommendation

Although the degree of confidence is a continuum, two categories are used: strong and weak.

A **strong recommendation** is one for which the panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects.

A **weak recommendation** is one for which the panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is not confident about these trade-offs. Reasons for not being confident can include:

- absence of high quality evidence;
- presence of imprecise estimates of benefits or harms;
- uncertainty or variation in how different individuals value the outcomes;
- small benefits;
- the benefits may not be worth the costs (including the costs of implementing the recommendation).

Strong vs. weak

- **Patients:** Most people in this situation would want the recommended course of action and only a small proportion would not
- **Clinicians:** Most patients should receive the recommended course of action
- **Policy makers:** The recommendation can be adapted as a policy in most situations

Differences

- Process is more explicit
- Uniform system of grading quality of evidence
- Specifies strength of recommendations
 - Strong: Do it or don't do it
 - Weak: Probably do it or probably don't do it
- Makes it easier for users to assess judgements behind recommendations

Revising the guidelines for managing children with severe malnutrition

- Review existing guidelines and determine potential areas for revisions
- Identify issues to be addressed and formulate as PICOT questions (**P**opulation, **I**ntervention, **C**ontrol, **O**utcome, **T**imeline)
- Systematic review with findings collated as GRADE tables
- Draft recommendations formulated (by internal WHO group)
- Guideline development group assesses draft recommendations according to:
 - systematic review
 - risk / benefit tables (incl. values, costing, feasibility)
- Confirm or revise draft recommendations
 - Allocate strength of recommendation
- Document and publish all materials and rationale for recommendations

NUGAG Work 2010-2011

Area acute malnutrition: SAM

1. Antibiotic treatment in children with SAM.
2. What are the implications of severe acute malnutrition on ART initiation and dosing?
3. Effectiveness and safety of vitamin A supplementation in children with SAM
4. Management of dehydration without shock due to diarrhoea (and vomiting) in children with SAM
5. Management of shock with IV fluids. in children with SAM
6. Blood or plasma transfusion in children with shock after failure of intravenous fluid in children with SAM
7. Feeding inpatient children with SAM and diarrhoea
8. Feeding outpatient children with SAM and diarrhoea
9. Feeding children with SAM in transition phase
10. Feeding the severely malnourished infants less than 6 months of age
11. Support to the mother/wet nurse for children under 6 months with SAM
12. Admission and discharge criteria for infants less than 6 months with SAM
13. Screening criteria for SAM children to be treated as outpatient
14. Discharge criteria for children over 6 months with SAM

Southampton systematic review

Southampton Health Technology Assessments Centre (SHTAC)

- What methods are effective for treating SAM among infants less than six months old?
- Which form of IV fluid administration is most effective for treating shock?
- What are the best treatments for children with SAM who have diarrhoea?
 - Composition of ORS for Mx of acute diarrhoea
 - Nutritional Mx of persistent diarrhoea
- What methods are effective in treating infection?
 - Antibiotics in inpatient settings
 - Antibiotics and RUTF vs. RUTF alone

Question: How best to feed the SM infant less than 6 mo of age (breastfed or non-breastfed infants)?

Settings: Inpatient SM infants less than 6 mo of age.

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
									Relative (95% CI)	Absolute		
2	Retrospective	+	-	+	+						Very low	
Mortality												10
							WHO guidelines for SM	other				
Nu Shwe et al. 1999	Retro cohort, with control	No baseline data given for 0-6mo age group				No statistical comparison carried out for this age group	Number of patients in this group not given in SR Year 1: 10.7% cases 0-6mo age group, proportional mortality 9.1% Year 2: 6.5% cases 0-6mo age group, proportional mortality 12.5%	Control year: 11.4% cases 0-6mo age group, proportional mortality 12%				
Weight gain												?
Hossain et al. 2009	Prospective cohort with concurrent control Local vs WHO protocol for treatment SAM						No reporting of number patients, or baseline characteristics in 0-6mo age group Mean weight gain 11.6 ±6.8g/kg/d	Mean weight gain 17.5 ±7.5g/kg/d	P=0.21			

Question: Management of shock with intravenous fluids in children with SM

Settings: All settings

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
									Relative (95% CI)	Absolute		
1		+			+						Low	
Mortality												10
							WHO fluid resuscitation regime (HSD/5D) N=26	Ringer's lactate N=29				
Akedi et al	Phase II equivalence RCT	Small number of patients				Small group of non-diarrhoeal shock allocated to HAS, dropped in analysis	15/26 in hospital mortality	13/29 in hospital mortality	p=0.34		Moderate	
Recovery from shock												9
	As above	as above				Outcomes only presented for survivors, not all those randomized	Shock unresolved at 8hr 15/22	Shock unresolved at 8hr 14/25	p=0.39			
Akedi et al							at 24hr 14/18	at 24hr 14/25	p=0.14			
							Oliguria (<1ml/kg/hr) at 8hrs 9/22	Oliguria at 8hrs 3/25	p=0.02			
							at 24hrs 8/18	at 24hrs 6/25	p=0.16		Moderate	
							Tachycardia (HR >160beats/min) at 8hrs 6/22	Tachycardia at 8hrs 4/25	p=0.34			
							At 24hrs 8/14	At 24hrs 4/25	p=0.04			

Participants and care-providers not blinded to treatment – no indication if assessor blinded. Trial prematurely terminated after interim safety review - underpowered

Question: Feeding children with SM and persistent diarrhoea

Settings: All settings

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
							Standard diet	Alternative	Relative (95% CI)	Absolute		
3		+			+	Not comparable					Very low	
Mortality												10
Amadi et al	RCT	Small number of patients					Neocate n=100 Mortality at 4wk n= 22	Standard diet n=100 Mortality at 4wk n= 17	p=0.48		Weak	
Nurko et al	RCT	Small number of patients				Comparison 3 diets	Chicken, n=15 Death n=2	Nursoy, n=13 Death n=1	Vivonex, n=13 Death n=2	Not reported	Strong	

Question: Feeding children with SM and persistent diarrhoea

Settings: All settings

Recovery from diarrhoea												6	
Nurko et al							Chicken, n=15 Mean stool output/kg/d±SD 19.1 ± 7.5 Mean day cessation ±SD = 6.9 ± 4.7	Nursoy, n=13 Mean stool output/kg/d±SD 18.5 ± 6.6 Mean day cessation ±SD = 3.9 ± 3.0	Vivonex, n=13 Mean stool output/kg/d±SD 18.8 ± 9.2 Mean day cessation ±SD = 8.0 ± 5.1	not sig			Weak
Bhutta et al		Small number of patients					Soy (n=21) Mean stool vol (g/kg/d±SD) Overall = 58 ± 33 Mean stool freq (n/d ±SD) Overall = 6 ± 3	Rice-lentils and yog (n=19) Mean stool vol (g/kg/d±SD) Overall = 62 ± 49 Mean stool freq (n/d ±SD) Overall = 6 ± 4	ns				
Adverse events/safety												8	
Nurko et al							Chicken, n=15 Some formula intolerance n=9 (47.4%) Treatment failure n=4 intestinal pneumatosis n= 1	Nursoy, n=13 Some fomula intolerance n=11 (57.9%) Treatment failure n=6 intestinal pneumatosis n= 1	Vivonex, n=13 Some formula intolerance n=14 (77.8%) Treatment failure n=5 intestinal pneumatosis n= 2	not sig not reported			Strong

Question: Antibiotic treatment in children with SM

Settings: All settings

Quality assessment							Summary of findings					Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect		Quality	
									Relative (95% CI)	Absolute		
1		+									Moderate	
Mortality												10
Dubray et al	Randomised, unblinded superiority-controlled trial	Participants and assessors not blinded					Ceftriaxone (IM, once per day for 2 days) N=228	Amoxicillin (80mg/kg/d, orally twice a day for 5 days) N=230				
							Death within 14 days of admission n=2 Total deaths to discharge n=7	Death within 14 days of admission n=8 Total deaths to discharge n=9	Not reported p=0.62			
Weight gain and recovery												8
Dubray et al	As above	As above					>10g/kg/d wt gain by d14 or discharge n= 127	>10g/kg/d wt gain by d14 or discharge n= 123	p=0.63			
							Mean overall wt gain (g/kg/d) = 11.4 (10.5-12.2)	Mean overall wt gain (g/kg/d) = 11.2 (10.2-11.9)	p=0.69			
							Mean length of stay (d) = 31.4 (29.4-33.3)	Mean length of stay (d) = 33.5 (31.5-35.5)	p=0.07			
Adverse events												8
Dubray et al	As above	As above					Adverse events (vomiting/diarrhoea) n= 2	Adverse events (vomiting/diarrhoea) n= 8	p=0.05			

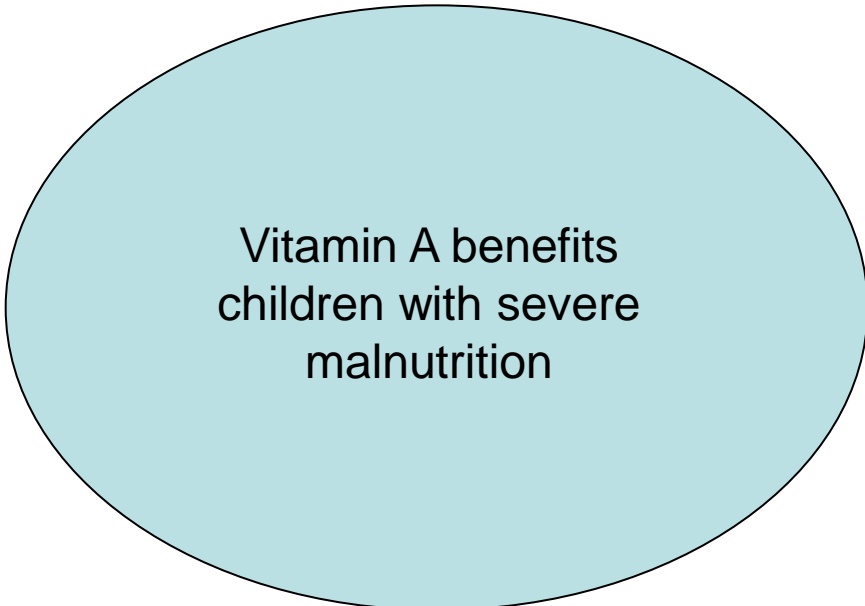
Other questions

- Timing of when to give vitamin A
- The role of blood transfusion if immediate resuscitation with crystalloids fails?
- How to feed children with diarrhoea and uncomplicated SM (outpatient)
- How to transition between feeds
- The child with HIV / living in an HIV prevalent area

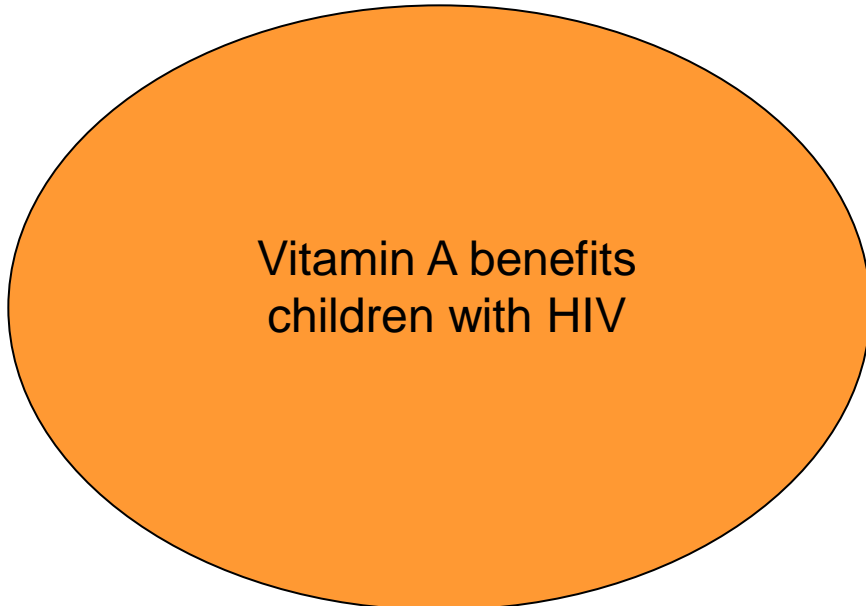


Limited data available on target population

- Extrapolating from other settings



Vitamin A benefits
children with severe
malnutrition

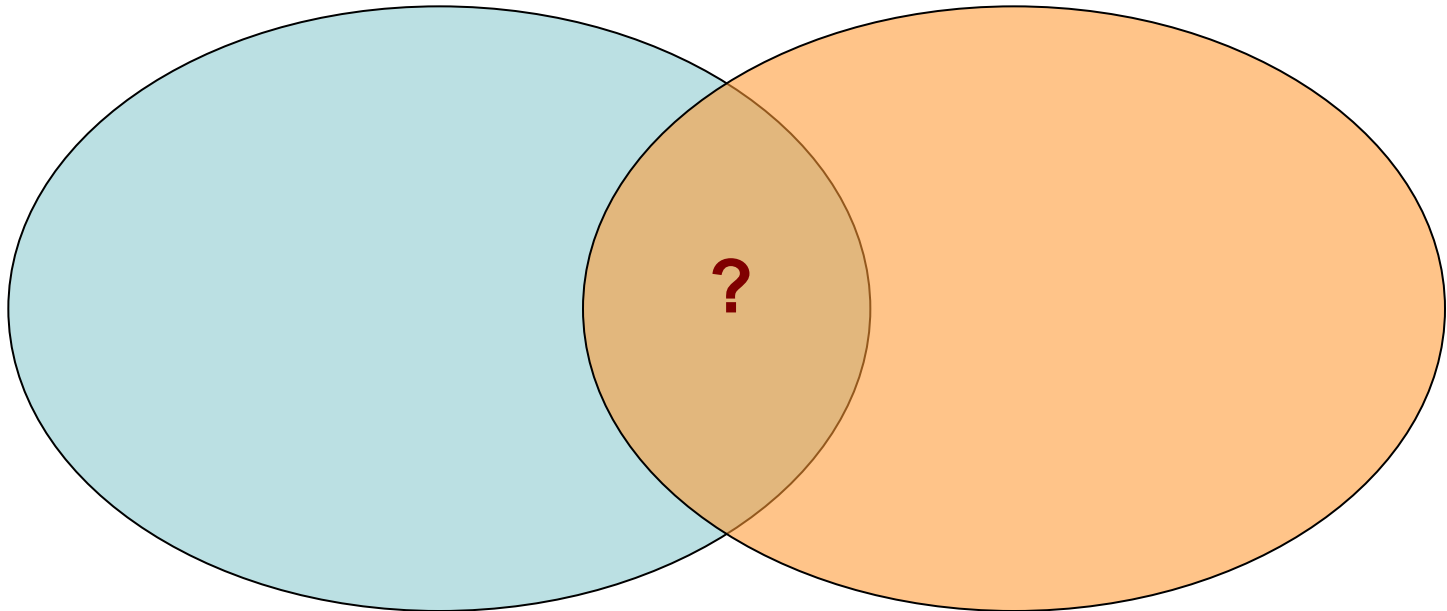


Vitamin A benefits
children with HIV

**No particular concern to recommend vitamin A
for HIV infected children with severe malnutrition**

Limited data available on target population

- Extrapolating from other settings



Problem areas

- Fluid management
- Infant less than 6 months
- Timing of initiation of antiretroviral treatment

Clinical care issues that are not amenable to *comparative research* but greatly influence care

- How to assess and monitor fluid status in the malnourished child?
- How to implement in local settings and maintain quality of care over time?
- Linking with prevention, and care after discharge in poor communities

November 2011 – early 2012

- Guideline development group meeting to review Grade summaries and to consider whether the evidence supports proposed new recommendations

→ **Summary of updated recommendations**

- *List of key research questions/priorities*

What will not be sorted

- Format and organization of guidelines to make them most useful when used by health workers
- Suggestions other than formal recommendations that also guide clinical practices

Role of CAPGAN

- Non-published programme data / practices that may inform guidelines
- Participate in guideline development
- Serve as an additional reference group after formulation of recommendations

Many thanks

Zita Weise Prinzo – weiseprinzoz@who.int

Nigel Rollins – rollinsn@who.int