

**Severe malnutrition:
Report of a consultation
to review current literature
6-7 September 2004**



**Nutrition for Health and Development
World Health Organization**

WHO Library Cataloguing-in-Publication Data

Informal Consultation to Review Current Literature on Management of Severe Malnutrition in Hospitals (2004 : Geneva, Switzerland)

Severe malnutrition : report of a consultation to review current literature.

1.Malnutrition - therapy 2.Infant nutrition disorders - therapy 3.Child nutrition disorders - therapy 4.Review literature 5.Guidelines I.Title.

ISBN 92 4 159331 8

(NLM Classification: WD 100)

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Printed in Switzerland

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Acknowledgements

The World Health Organization (WHO) gratefully acknowledges the contributions of Professor Ann Ashworth for preparing the report, Professor Alan Jackson for chairing the Consultation and for his contributions throughout the preparation of the report, and Professor David Brewster for writing the critical review paper. Thanks are also due to Dr Tahmeed Ahmed, Dr James Bunn, Professor Michael Golden, Dr G.T. Heikens, Professor Michael Krawinkel, Professor Nigel Rollins and Dr Gareth Tudor Williams, for their presentations and Dr Bruce Cogill, Food and Nutrition Technical Assistance (FANTA) project and Mrs Susie Villeneuve, United Nations Children's Fund (UNICEF) for their comments and support.

Special thanks are extended to Dr Sultana Khanum for overall coordination and technical contributions. Thanks are also due to Ms Zita Weise Prinzo and Mrs Randa Saadeh, Department of Nutrition for Health and Development, Dr Siobhan Crowley, Department of HIV/AIDS, 3 × 5 Programme, Dr Martin Weber and Dr André Briend, Department of Child and Adolescent Health and Development, for their technical inputs and comments.

This report and the Consultation were made possible through the support provided to the FANTA Project by the Office of Health, Infectious Diseases and Nutrition of the Bureau for Global Health at the US Agency for International Development, under terms of Cooperative Agreement No. HRN-A-00-98-00046-00 awarded to the Academy for Educational Development (AED). The opinions expressed herein are those of the authors and do not necessarily reflect the views of the US Agency for International Development.

EXECUTIVE SUMMARY

The World Health Organization (WHO), together with international experts, has developed two manuals for the management of severe malnutrition. These are *Management of severe malnutrition: a manual for physicians and other senior health workers* (WHO, 1999), and its abbreviated form in chapter 7 of *Integrated Management of Childhood Illnesses (IMCI) Management of the child with a serious infection or severe malnutrition: guidelines for care at the first-referral level in developing countries* (WHO, 2000). The more recent of these two manuals was sent to 83 peer reviewers in 1998. There was consensus that the guidelines were technically correct.

These sets of guidelines are for doctors, senior nurses and other senior health professionals responsible for the care of young children in hospitals at the first-referral level in developing countries. A guiding principle in their development was that they should be able to be implemented with basic resources and limited staff. The aim of the guidelines on malnutrition is to improve case-management so that the high case-fatality rates that occur in many hospitals are substantially reduced. Evidence is accruing to indicate that this is an achievable goal.

Objectives

The objectives of the Consultation that took place in Geneva from 6 – 7 September 2004 were to:

1. critically review new evidence in relation to the current WHO guidelines;
2. consider if changes to the guidelines may be required as a result of the new evidence;
3. consider if the guidelines for infants aged < 6 months should be modified;
4. assess the guidelines in relation to care of severely malnourished children with Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS)

- or children of unknown status in areas where there is a high prevalence of HIV; and
5. identify a research agenda for inpatient care of severely malnourished children.

Knowledge reaffirmed by the Consultation

- that the underlying conceptual framework to the WHO guidelines is robust and critical to a successful outcome;
- that this structured approach to care involves 10 steps in two phases and takes into account the profound physiological changes that occur in children with severe malnutrition;
- that, given a minimal health infrastructure, effective implementation can be achieved when the available staff are trained and supported to follow the guidelines and make the best use of limited resources;
- that implementation leads to improved case-management and fewer deaths; and
- that there is an urgent need to train and support hospital staff and other relevant health professionals to implement the WHO guidelines.

Critical review of new evidence

The Consultation identified only limited peer-reviewed new research for the period under review (1998–2004), in which severely malnourished children had been studied. During this period, however, substantial advances in knowledge about HIV/AIDS have occurred, and there is now increased opportunity for HIV-testing and antiretroviral therapy. These changes will have programmatic implications for the care of severely malnourished HIV-infected children in the future.

No new research was identified pertaining to the optimum dietary management of severely malnourished infants aged < 6 months. The evidence base for defining the most advantageous formulations for feeding this age group remains weak.

Programmatic changes identified

For severely malnourished HIV-positive children:

- staphylococcal and Gram-negative cover (e.g. ampicillin and gentamicin) is essential for severe pneumonia as HIV-positive children have a wide range of pathogens. For pneumonia with severe hypoxia, *Pneumocystis* pneumonia should be considered and high-dose cotrimoxazole added to the treatment regimen (see section 3.4.1.2);
- children aged < 15 months who test positive for HIV antibodies by the enzyme-linked immunosorbent assay (ELISA) but whose HIV status has not been confirmed, or have not been tested, but are known to have been exposed to HIV infection, should receive prophylactic cotrimoxazole from the time of admission and throughout their hospital stay to reduce the risk of contracting *Pneumocystis* pneumonia and other infections. They should continue to receive prophylactic cotrimoxazole after discharge until their infective state is either confirmed or excluded (e.g. by re-testing by ELISA at age > 15 months). For children who are known to be infected with HIV, prophylactic cotrimoxazole should be continued indefinitely (see section 3.4.1.2); and
- children who are repeatedly admitted for advanced disease should not receive the high dose of vitamin A on day 1 of every repeat admission. They should receive it only if there has been an interval of at least 4 months since they received the last high dose (see section 3.4.2).

Facilitating implementation

The following measures should be noted for the facilitation of implementation:

- Provision of potassium is vital for all severely malnourished children, but in some areas it may be difficult to obtain potassium chloride or the combined mineral–vitamin mix (CMV). In such areas, slow-release potassium tablets, which are widely available, may be substituted (see section 3.5).

- Changes have been made to the recipe for preparing low sodium oral rehydration solution for malnutrition (ReSoMal) from the new WHO 75 mmolNa/L ORS sachet (see section 3.6).

Research agenda

There are still gaps in knowledge in several areas, particularly in relation to feeding very young infants and to caring for children living with HIV/AIDS. Given the lack of published information regarding the most advantageous formulations for feeding severely malnourished infants aged < 6 months, there is a need for observational studies and comparative randomized trials of alternative formulations to guide decisions about optimum dietary management in this age group. As yet there are no published studies of the effectiveness of antiretroviral therapy or micronutrient or energy supplementation in severely malnourished children who are HIV-positive and few studies in children who are not malnourished. Information is needed on the pharmacodynamics of different drugs and regimens in severely malnourished infants and children. The level of immunosuppression and the phase of malnutrition treatment at which to start antiretroviral therapy also need clarification.

The development of a defined plan of research is encouraged to fill the knowledge gaps and achieve a clearer understanding of optimum case-management. On the assumption that this research is carried out, it might be anticipated that a major review of the guidelines would be needed in the future. The year 2010 was suggested as a reasonable target for completion of this task.

Conclusion

In developing countries, implementation of the WHO guidelines for inpatient management of children with severe malnutrition can reduce child deaths substantially and make a major contribution to achieving the Millennium Development Goal of improved child

survival. Current coverage of the guidelines is poor and will need to be scaled up.

The Consultation has served to emphasize the importance of having a formal mechanism through which a reliable evidence-base, suitable for guiding policy, could be generated, and through which future advances in understanding might be incorporated into guidelines in a timely way.

The next steps will be:

- a wider meeting with key partners to share the conclusions of this Consultation with a view to consolidating implementation of the WHO guidelines and broadening the research base;
- a planning meeting to consider the remit, structure and potential value of a Technical Advisory Group, and the logistics of establishing a web-based information forum; and
- preparation of an additional module for the WHO Training Course on Improving Treatment of Severe Malnutrition. This module will focus on the treatment of severely malnourished children living with HIV/AIDS and will include the programmatic changes highlighted in this report.

1. BACKGROUND

The World Health Organization (WHO), together with international experts, has developed two manuals for the management of severe malnutrition. These are *Management of severe malnutrition: a manual for physicians and other senior health workers (1)* which was published in 1999, and its abbreviated form in chapter 7 of *IMCI Management of the child with a serious infection or severe malnutrition: guidelines for care at the first-referral level in developing countries (2)*, published in 2000. The more recent of these two manuals was sent to 83 peer reviewers in 1998. These manuals are referred to as "guidelines" throughout the report. There was consensus that the guidelines were technically correct.

The guidelines are for the use of doctors, senior nurses and other senior health professionals responsible for the care of young children in hospitals at the first-referral level in developing countries. A guiding principle in the development of these guidelines was that they should be able to be implemented with basic resources and limited staff. The aim of the malnutrition guidelines is to improve case-management so that the high case-fatality rates that occur in many hospitals are substantially reduced (for example to < 5% in areas with low prevalence of human immunodeficiency virus (HIV)). Evidence is accruing to indicate that this is an achievable goal.

2. OBJECTIVES

In addition to reviewing new research findings, this Consultation was called by WHO, Geneva to consider case-management of two subgroups of children, namely:

- severely malnourished infants aged < 6 months; and
- severely malnourished children living with HIV or acquired immunodeficiency syndrome (AIDS);

and to consider whether they may require different or additional treatment from that given in the guidelines.

Thus the objectives of the Consultation were to:

1. critically review new evidence in relation to current guidelines;
2. consider if changes to the guidelines may be required as a result of the new evidence,
3. consider if the guidelines for infants aged < 6 months should be modified;
4. assess the guidelines in relation to care of severely malnourished children with HIV/AIDS, or children of unknown status in areas where there is a high prevalence of HIV; and
5. identify a research agenda for inpatient care of severely malnourished children.

The use of ready-to-use therapeutic food (RUTF) was purposely omitted from the agenda as the guidelines already make provision for its use as an alternative to the milk-based catch-up formula F100 in the rehabilitation phase. (The agenda items and names of participants are given in Annex 1 and 2, respectively.)

3. FINDINGS

3.1 Progress in reducing deaths from severe malnutrition

Severe malnutrition is defined in the guidelines as severe wasting (< 70% weight-for-length or <-3SD) and/or oedema. Where the WHO guidelines have been implemented as recommended, substantial reductions in case-fatality rates have been achieved. For example, in hospitals in Myanmar, deaths have been halved among severely malnourished children coincident with improved case-management, and in emergency situations very low case-fatality rates are being achieved. Development and adoption of the guidelines thus represent a substantial step towards reducing the

unacceptably high case-fatality rates that currently exist in many countries. The need now is for implementation to be widened through in-service training and incorporation of the guidelines into medical and nursing curricula. Implementation has the potential to save many of the lives currently being lost through severe malnutrition and to contribute substantially to achieving the Millennium Development Goal of reducing childhood mortality. Implementation of the guidelines has been shown to be feasible and sustainable even in small district hospitals with limited resources (3, 4). Specific constraints which limit the effective delivery of enhanced care include lack of resources (e.g. of electrolyte/mineral mix), inadequate professional training, lack of commitment and poor health system infrastructure.

The Consultation reaffirmed that the underlying conceptual framework to the guidelines is robust and critical to a successful outcome. This structured approach to care involves 10 steps in two phases (stabilization and rehabilitation) and takes into account the profound physiological changes that occur in children with severe malnutrition.

3.2 New research findings

The Consultation identified only limited peer-reviewed new research for the period under review (1998–2004), in which severely malnourished children had been studied. During this time, however, substantial advances in knowledge about HIV/AIDS have been made, and there is now increased opportunity for HIV-testing and antiretroviral therapy. These changes will have programmatic implications for the care of severely malnourished children with HIV infection.

Within the overall framework for the care of severely malnourished children, gaps in knowledge were identified, and it was accepted that a defined plan of research should be developed to fill them and to achieve a clearer understanding of optimum case-management. There was wide agreement that this should be a

continuing process through which relevant research could be commissioned and new evidence assessed. It was accepted that there may be areas of the world where context-specific modifications could be needed. On the assumption that this research is carried out, it might be anticipated that a major review of the guidelines would be needed in the future, and the year 2010 was suggested as a reasonable target for completion of this task.

3.3 Infants aged less than 6 months

The guidelines were not developed with active consideration of the needs of young infants below 6 months of age: their nutrient requirements are different and their physiological processes less mature than those of older infants. This group is also more heterogeneous in terms of underlying etiology and pathophysiology than older infants. The Consultation reaffirmed that the 10-step approach does apply to these young infants, but that consideration needs to be given to the type of feed and volume given. The guidelines recommend F75 milk formula for feeding in the stabilization phase and F100 for the rehabilitation phase. The potential renal solute load (PRSL) of these and other milk formulations was the focus for discussion.

3.3.1 Potential renal solute load: The PRSL refers to solutes of dietary origin that would need to be excreted in the urine if none was diverted into new tissue or lost through extrarenal routes. The PRSL is estimated by summing dietary nitrogen expressed as millimoles of urea (i.e. mgN/28) and the millimoles of dietary sodium, potassium, chloride and available phosphorus. Excretion of urea contributes most to the renal solute load, so the higher the protein intake the greater the amount of solute produced. For excretion by the kidney, urea and other solutes must be in solution, and this requires water. Healthy infants are able to maintain their water balance, but if situations arise where water is being lost through, for example, high fever, diarrhoea, or excessive evaporative loss in hot dry climates, there is a risk of negative water balance and hypernatraemic dehydration. In the

United Kingdom and the USA, the prevalence of hypernatraemic dehydration fell in response to a shift from feeding infants with whole cow's milk and evaporated milk to feeding with infant formula, and there are now recommended upper limits for PRSL (5).

Severely malnourished children have a reduced capacity to concentrate urine. The same also applies to very young infants. The estimated PRSL of F75 falls within the range that is considered safe. (This will be discussed further below.) During rapid growth, solutes are deposited in lean tissue (estimated at 0.9 mmol of PRSL per g weight gain) and so a lower proportion will require excretion. Thus, during the rehabilitation phase when rates of tissue deposition are extremely rapid, the actual renal solute load of F100 can be expected to be considerably less than the estimated potential load. A difference of opinion and practice has arisen regarding F100. On the one hand, some consider that it is inappropriate to advocate the use of any formulation that would not be allowed in Europe or the USA for well-nourished infants under 6 months of age. Consequently some workers advocate diluting F100 by one-third to lower the renal solute load. Others take the view that because severely malnourished infants gain weight more rapidly than healthy infants, the risk of dehydration with F100 is theoretical rather than real. Clinical experiences in the field with diluted F100 appear to be inconsistent; some have reported good weight gains and others static weights. No relevant published reports had been identified in the literature.

The Consultation reviewed the estimated PRSLs for human milk, infant formula, F75, F100 and diluted F100 calculated according to Fomon & Ziegler (6) (Table 1).

Table 1. Estimated potential renal solute loads of human milk and infant formulas

<i>Type of milk</i>	<i>Estimated PRSL (mOsmol/L)</i>
Human milk	93

Milk-based infant formulas	135–177
F75	154
F100	360
Diluted F100	238

The maximum value for PRSL proposed for well-nourished children by the Life Sciences Research Office (LSRO) of North America is 33 mOsmol/100 kcal (equivalent to 223 mOsmol/L) (5). Based on the risk of hypernatraemic dehydration, it has been proposed that feeding a formula with a PRSL of 176 mOsmol/L (26 mOsmol/100 kcal) or less affords an adequate margin of safety with respect to water balance, whereas feeding a formula providing 263 mOsmol/L (39 mOsmol/100 kcal), or more, predisposes the infant to hypernatraemic dehydration (5, 6). The above-mentioned figures indicate that F75 has an estimated PRSL below the maximum proposed for healthy infants growing normally, and that diluted F100 is marginal. For F100, the estimated PRSL exceeds the maximum, but no adjustment has been made to allow for rapid tissue deposition in severely malnourished children which lowers the actual renal solute load. The situation regarding the safety of F100 for infants aged < 6 months who are gaining weight rapidly is therefore unclear. Concern was also expressed that the composition of F75 may not be perfectly matched to the needs of very young, severely malnourished infants.

3.3.2 Appropriateness of the guidelines for infants aged less than 6 months

Given the lack of published evidence regarding the most advantageous formulations for feeding severely malnourished infants aged < 6 months, there was strong agreement on the need to conduct observational studies and comparative randomized trials of alternative formulations to guide decisions about optimum dietary management in this age group. The Consultation agreed that because these infants are at special risk of water stress in situations where there might be a significant increase in non-renal water losses, through for example increased losses in sweat

in hot, dry climates, special care needs to be taken with any formulation that might lead to a high PRSL in infants who are not gaining weight rapidly. Given the limitations of current knowledge, but mindful of the need to guide health workers in the interim, and bearing in mind directives as to PRSL in healthy children, the Consultation broadly agreed the following:

Stabilization phase. The Consultation proposed that until definitive data are forthcoming, the guidelines set out for stabilization with F75 should be followed for infants under 6 months of age. Diluted F100 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 F75.

Rehabilitation phase. The actual renal solute load is related to the rate of weight gain. The PRSL is high for F100 and some members of the Consultation felt it should not be used as its PRSL exceeds the upper limit recommended by LSRO. Some felt that F100 should not be used for infants < 4 months of age. Expressed breast milk, infant formula or diluted F100 were seen as possible alternatives. Others considered that F100 may be appropriate if weight gain is rapid. The results of comparative randomized trials will guide future decisions about appropriate formulations for feeding infants under 6 months of age.

Breastfeeding. The Consultation agreed that human milk is the preferred food for young infants, although in HIV-affected populations decisions about breastfeeding are complex. The Consultation agreed that in infants with severe malnutrition, who are acutely and severely ill, resuscitation and stabilization with therapeutic milk take precedence over breastfeeding. Participants reported that in Bangladesh and Sierra Leone, exclusive breastfeeding in managing severe malnutrition had been unsuccessful, resulting in the deaths of infants. Experience has also shown that when no effort is made to re-establish successful lactation, infants often end fully weaned, which can compromise

their longer-term survival. Therapeutic feeding combined, where appropriate, with supportive care to re-establish successful lactation, is recommended. Supportive care is described in *IMCI Management of the child with a serious infection or severe malnutrition: guidelines for care at the first-referral level in developing countries* (99–104) (2).

Low-birth-weight infants. The Consultation clarified that low-birth-weight infants who are *not* severely wasted or oedematous should be managed according to guidelines provided by WHO specifically for such infants (7, 8).

3.4 Children living with HIV/AIDS

Knowledge of the HIV virus and the opportunities for HIV testing have increased since the guidelines were originally published, as has the availability of antiretroviral drugs (ARVs). It is well-established that the HIV virus mutates and replicates extremely rapidly (10^9 new virions/day), and that very high destruction rates of CD4 T-lymphocytes occur even in individuals who are asymptomatic. Controlling viral replication is therefore essential. For adults starting treatment with triple-drug ARVs, the median time taken for the viral load to decrease to undetectable levels is 12 weeks. For children it may take 24 weeks as they tend to start with higher viral loads. Restoration of the immune system, however, takes much longer. The most effective combinations of drugs act at different sites, for example drugs such as nevirapine (a non-nucleoside reverse transcriptase inhibitor) latch on to the active site of the viral reverse transcriptase and stop it from building DNA from RNA, whereas drugs such as azidothymidine (AZT) (a nucleoside reverse transcriptase inhibitor) latch on to new strands of DNA and act as chain terminators. Protease inhibitors, on the other hand, attack the final stages of viral replication by preventing the assembly of the viral components into new HIV viruses. The CD4 cell count is a marker of the degree of immunosuppression and is used in deciding when to start ARV therapy. In children, the CD4 cell count is best

expressed as a percentage of total T-cells (CD4%), rather than the absolute count, as it varies less with age. Where access to CD4 cell counts is limited, a useful proxy is the total lymphocyte count.

The ELISA assay is routinely used for detecting HIV antibodies, but is reliable only in children aged > 15 months as younger uninfected children could still test positive as a result of the presence of maternal antibodies. Definitive testing for the virus (e.g. western blot or molecular (polymerase-chain reaction (PCR)) techniques) is expensive.

The statements in the Manual (*I*) that severely malnourished children “should not be tested routinely for HIV”, or if tested “the results should not be revealed to the staff”, are no longer applicable, and do not appear in the WHO-IMCI guidelines. HIV testing has clear benefits even where ARVs are unavailable, for example in identifying children to whom prophylactic cotrimoxazole should be given.

3.4.1 Severe malnutrition associated with HIV/AIDS

The approach to treatment of severe malnutrition associated with HIV/AIDS will be determined by a number of factors, of which the following are of particular importance:

- knowledge of HIV status and CD4 cell count (or total lymphocyte count);
- availability of ARVs; and
- presence of comorbidities or secondary infections.

As regards HIV status, there are three different situations that would influence the treatment of a severely malnourished child.

1. Mother is known to be HIV-infected, but the child is HIV-negative. For those children who become severely malnourished, the approach is to follow the guidelines for severe malnutrition.
2. Child is HIV-infected, and the CD4 count is not low. The approach is to follow the guidelines for severe malnutrition, taking into account the changes set out in the

following section (3.4.1.2) pertaining to the prevention and treatment of comorbidities.

3. Child is HIV-infected and meets national criteria for ARV therapy (either by CD4% or clinical staging). In this case, the approach is to treat with ARVs and to follow the guidelines for severe malnutrition.

Currently the best approach for ARV therapy is not clear. The choice will depend upon availability, local protocols and better information on the pharmacodynamics of different drugs and regimens in infants and children in general, and in severely malnourished infants in particular. The level of immunosuppression (e.g. CD4%) and the phase of malnutrition treatment at which to start ARV therapy also need to be determined.

As yet there are no published studies of the effectiveness of treatment with ARVs in severely malnourished children and few studies of their use in children who are not malnourished. The results in children who are not malnourished appear promising and generic drug companies are starting to produce infant/junior formulations. Children who are not malnourished metabolize ARVs faster than adults and need higher doses per kilogram of body weight to achieve adequate drug concentrations. The pharmacokinetics and safety of ARVs in severely malnourished children have yet to be studied. ARVs may have side-effects that may affect adherence to medication and efficacy. Potential short-term adverse consequences include nausea, diarrhoea, liver damage, bone marrow suppression and pancreatitis. Longer-term adverse effects include mitochondrial toxicities, metabolic complications, anaemia and neutropenia. Doses of ARVs must be increased as the child's weight increases, otherwise resistance is likely to develop. Immune reconstitution inflammatory syndromes may occur in the early months after commencing ARV therapy. Difficulties are anticipated in treating children who are already anorexic or have severe mouth lesions from thrush, impaired absorption or abnormal drug metabolism. There are also practical

problems in that some liquid formulations have an unpleasant taste and tablets may not be of an appropriate dose for small children, and important interactions may occur between ARVs and other drugs, for example with rifampicin being given for tuberculosis. In addition to the high costs of the drugs (currently higher in children than adults), ARV treatment entails continuous monitoring, which requires additional human and financial resources. Follow-up of children with malnutrition is variable, but will need to be exemplary if ARVs are to be successful. Food and/or micronutrient supplementation is likely to be important and may modify pharmacokinetics, drug side-effects and adherence. Nevertheless, ARV treatment of children has already started in some countries, for example, Botswana and Zambia, and it is expected that the use of ARVs will increase. The position of the Joint United Nations Programme on HIV/AIDS (UNAIDS) is that ARVs should be used in adults and that children should not be excluded from being given the opportunity to benefit from this treatment.

3.4.1.1 Comorbidities

HIV infection is often combined with other infections and conditions. Anorexia and diarrhoea are common in children with HIV and in those with severe malnutrition. Gut enteropathy tends to be worse in HIV-infected children than in uninfected children. Children with advanced HIV disease who have profound anorexia may benefit from continuous feeding through a naso-gastric tube. Children with monosaccharide and disaccharide intolerance (diagnosed by anhydrous Benedict's reagent, e.g. Clinitest tablets or glucose dipstick in watery stools) may benefit from preparing F75 or F100 with lactose-free ingredients. Despite more protracted diarrhoea in HIV-positive children, stool pathogens are similar to those in HIV-negative children. *Cryptosporidium parvum* infection in seropositive children is an important cause of enteropathy and may result in protracted diarrhoea and malabsorption. It was suggested that routine administration of metronidazole may help repair gut damage in malnourished

children with symptomatic HIV, but there have been no clinical trials to guide policy.

3.4.1.2 Secondary infections

Disease progression is more rapid in HIV-infected children than in adults and they suffer opportunistic infections more frequently. In young children the most common opportunistic infection is *Pneumocystis jiroveci* pneumonia (PCP) (formerly *P. carinii*), especially in infants aged 2–6 months. Most infections and deaths, however, are caused by the same pathogens as are found in HIV-negative children.

Severe pneumonia. In the case-management guidelines for severe malnutrition, the stated treatment for severe pneumonia (rapid breathing + chest indrawing) is with intramuscular benzyl penicillin for 5 days. This may be insufficient in children with HIV in whom there is a wider range of causative organisms, including Gram-negative bacteria. The Consultation agreed that adequate staphylococcal and Gram-negative cover (e.g. ampicillin and gentamicin) is essential for treatment of severe pneumonia in children with HIV. If severe hypoxia is present suggestive of *Pneumocystis jiroveci*, high-dose cotrimoxazole is also needed as described in *IMCI Management of the child with a serious infection or severe malnutrition: guidelines for care at the first-referral level in developing countries* (2, p. 94).

Respiratory infections (including PCP) can be prevented by prophylaxis with cotrimoxazole. In the recent CHAP trial, survival of HIV-infected children was greatly enhanced by long-term prophylactic administration of cotrimoxazole (9). The Consultation agreed that children aged < 15 months who test positive by the ELISA antibody assay but whose HIV status has not been confirmed; or are untested, but are known to have been exposed to HIV infection, should receive prophylactic cotrimoxazole from the time of admission and throughout their hospital stay. They should continue to receive prophylactic cotrimoxazole after discharge until their HIV status is either

confirmed or excluded (e.g. by re-testing by ELISA at age > 15 months). For children who are known to be HIV-infected, prophylactic cotrimoxazole should be continued indefinitely.

Tuberculosis. The diagnosis of tuberculosis (TB) is difficult in children because sputum specimens are not easy to obtain and laboratory methods for detecting disease have low sensitivity. Failure to gain weight over 2 weeks is often taken as a sign of TB, but poor weight gain can be (and often is) due to inadequate dietary intake. Diagnosis is thus prone to error, especially in children with HIV, and there is a potential for mistreatment. The Edwards score for identifying TB performs poorly in children with HIV. Improved scoring systems to aid recognition and diagnosis are needed. There is also the risk that HIV-infected mothers may bring TB onto the ward, raising the question as to whether TB prophylaxis might be desirable, but this was not considered appropriate. WHO has recently updated its TB treatment guidelines in *Treatment of tuberculosis: guidelines for national programmes* (10).

Other common opportunistic infections. These include oral and oesophageal candidiasis, herpes stomatitis and cytomegalovirus (diagnosis and treatment difficult). Bacterial infections are common in children with severe malnutrition irrespective of their HIV status, but HIV-positive children are more prone to severe bacterial infection than HIV-negative children. The most frequent causative agents in HIV-positive children are *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (11). Another common cause of severe infection is non-typhoidal *Salmonella* spp.

The Consultation noted that:

- Fluconazole is the preferred treatment for oesophageal and resistant oral thrush, and causes less liver toxicity than ketoconazole. Fluconazole is now on the WHO Model List of Essential Medicines and is increasingly available.

- Steroids should not be prescribed for mild or moderate lymphoid interstitial pneumonitis (LIP) as they suppress immune function and may increase the risk of opportunistic infections and tuberculosis. Steroids should only be given for severe LIP as specifically set out in *IMCI Management of the child with a serious infection or severe malnutrition: guidelines for care at the first-referral level in developing countries* (2, p. 95).
- Antibiotic drug resistance is an escalating problem and procedures need to be put in place at the national level to keep health professionals up to date with local resistance patterns, and to modify the medication guidelines to reflect the local context.

3.4.2 Diet and nutrients

Interventions in industrialized countries for adults with AIDS indicate only marginal benefit from the use of appetite stimulants, nutritional support, total parenteral nutrition and IGF-1, in the absence of ARV therapy. These populations, however, are food secure and are less likely to have nutritional deficiencies than populations in poor communities. The targets for energy and protein intakes set out in the guidelines were considered appropriate, and there is experience that severely malnourished children with HIV, including those with persistent diarrhoea, can gain weight when they are adequately fed (i.e. fed according to the guidelines).

Breastfeeding. In HIV-affected populations, mothers may have already opted for replacement feeding, so statements in the Manual (1) that children should continue to be breastfed may be inappropriate. (*Note:* these outdated statements do not appear in the WHO-IMCI guidelines.)

Micronutrient supplementation in HIV-infected children. The effects of severe malnutrition on immune suppression are similar to those of HIV infection. Deficiencies of micronutrients adversely affect immune function, especially deficiencies of

antioxidant nutrients such as zinc and selenium, and vitamins A, C and E. In observational studies of HIV-infected adults, micronutrient deficiencies have been associated with faster disease progression, increased mortality and higher risks of HIV transmission. It has been proposed that oxidative stress resulting from micronutrient deficiency may accelerate immune cell death and viral replication. In the Cochrane review of 32 micronutrient supplementation trials, the results (on viral load, CD4 cell counts, all-cause mortality and comorbidity) were mixed, and many trials reported no benefit. The first double-blind placebo-controlled randomized mortality trial of multi-micronutrients in HIV-infected adults not receiving ARVs was reported in 2003 from Thailand (12). At the end of 48 weeks, survival was increased in a subset of adults with low initial CD4 cell counts ($< 200 \text{ cells} \times 10^6/\text{L}$) although their CD4 cell count and viral load did not improve. More recently in the United Republic of Tanzania, however, multivitamin supplementation of pregnant women infected with HIV did improve CD4 cell counts and reduce viral load, and there was delayed disease progression and fewer complications from candidiasis and diarrhoea (13).

Very few trials of micronutrient supplementation have been conducted in children with HIV; none is robust and there is no clear evidence that supplementation slows disease progression. In South Africa, supplementation with high-dose vitamin A at 1, 3, 6, 9, 12 and 15 months reduced diarrhoea in HIV-positive infants by 49% and hospitalization for diarrhoea by 77% (14). In the United Republic of Tanzania, vitamin A supplementation reduced all-cause mortality by 63% in HIV-infected children admitted to hospital with pneumonia (15).

The malnutrition guidelines advise that all severely malnourished children receive multivitamins, zinc and copper daily for at least 2 weeks. In the rehabilitation phase iron is also given. Where the combined mineral–vitamin mix (CMV) is used, additional trace elements including selenium are provided. The Consultation considered that for the time being the guidelines regarding daily

micronutrients should be followed for all children with severe malnutrition, regardless of their HIV status. As new evidence emerges, changes to the guidelines may be appropriate.

The guidelines also advise the administration of a single high dose of vitamin A on admission. Repeated dosing needs to be approached cautiously for children with symptomatic HIV and others who are continually being readmitted, and the Consultation proposed that the high dose be given to readmitted children only if there has been an interval of at least 4 months since the last high dose.

Advice in the WHO-IMCI guidelines (2) (pp. 92-98) should be followed regarding testing for HIV, management of HIV-related conditions, follow-up and palliative care. As for all children, the weights of those living with HIV/AIDS should be diligently monitored and action taken immediately if a child loses weight to prevent relapse to severe malnutrition.

3.5 Vitamin A, potassium, phosphorus and cysteine

The Consultation considered six papers (16–21), and an editorial (22) relating to studies on vitamin A, potassium, phosphorus and cysteine.

Vitamin A. Deficiency of vitamin A has traditionally been seen as one of the most common deficiencies associated with severe malnutrition. Three important functions relate to host immune responses, mucosal integrity and vision. Infections, especially measles, increase the utilization of vitamin A. The guidelines advise a high dose of vitamin A on day 1, followed by small daily doses.

One paper (16), one letter (17) and one abstract (18) were considered. The aim of the studies was to compare the efficacy of

a single high dose of vitamin A with that of a daily low-dose regimen on morbidity (16), duration of diarrhoea (17), and morbidity and mortality (18). The high dose of vitamin A was 200 000 IU (or 100 000 for infants aged < 12 months (16, 17)). A low dose was 5 000 IU. The hypothesis was that daily doses would be more efficacious than an initial high dose as vitamin A absorption may be blunted on admission (16). In the Democratic Republic of Congo, 900 consecutive paediatric admissions were randomly assigned to receive either a high dose of vitamin A on admission, daily low doses or a placebo, during their hospital stay (16). Mortality in the high, low and placebo groups was 8.0%, 8.4% and 8.9%, respectively (NS). There were no significant differences between the groups in duration of diarrhoea or the incidence of nosocomial fever, respiratory infections or moderate diarrhoea. For severe nosocomial diarrhoea in a subset of oedematous children, the incidence in the high-dose group was similar to that in the placebo group, but the incidence was significantly lower in the children who received daily low doses than those who received the placebo (RR, 0.21; 95% CI, 0.07–0.62; $P = 0.005$).

In Senegal (17), 205 children with persistent diarrhoea were randomly assigned to receive either a high dose of vitamin A on admission or daily small doses for up to 60 days. Mortality in the high- and low-dose groups was 16.8% and 12.4% respectively (NS), and duration of diarrhoea was similar in both groups.

In another study in Senegal (18), 1214 children (consecutive paediatric admissions) received either a high dose of vitamin A on admission or daily low doses. Mortality was 11.1% and 9.7% in the high- and low-dose groups, respectively (NS). In a subset of oedematous children, mortality in the group that received a daily low dose was significantly lower than in the high-dose group (OR, 0.21; 95% CI, 0.05–0.99).

The discussions touched on the lack of convincing evidence for an effect of vitamin A on measles mortality in the Cochrane review,

the good absorption of vitamin A in severely malnourished South African children, and the problem of using the serum concentration of vitamin A as an indicator of deficiency, because the concentration of retinol-binding protein falls during an acute infection. Prevention of blindness was raised as an important consideration in vitamin A dosing. In Bangladesh, oedematous children with clinical signs of vitamin A deficiency are more likely than wasted children to progress to keratomalacia, as a result of lower levels of retinol-binding protein.

Interpretation of the three studies in relation to the guidelines was considered difficult and their validity was thought to be doubtful. For example, the vitamin A regimens studied did not replicate those in the malnutrition guidelines (which advocate a single high dose followed by daily low doses) and case-management is not described in the studies.. It was accepted that the question of vitamin A dosage is an important one and that there is scope for further research.

Potassium. Low body potassium is ubiquitous in individuals with severe malnutrition and can have fatal consequences. High priority is given in the guidelines to the provision of potassium, either as an electrolyte/mineral solution or in CMV. Correction of potassium deficiency within cells is rapid (about 1 week). Repletion of total body potassium takes longer (about 4 weeks) as this requires tissue accretion. One paper (19) was discussed. In Malawi, 99 oedematous children were randomly assigned to receive either extra potassium (3 mmol/kg/day) or a placebo for the first 7 days of treatment.

- Phase 1 (stabilization): 4.7 mmol (as in the Manual) versus 7.7 mmol/kg/day (3 mmol extra (i.e. $4.7 + 3 = 7.7$ mmol/kg/day); and
- Phase 2 (rehabilitation): as in the Manual (7.6 mmol/kg/day).

The hypothesis was that the extra potassium would hasten oedema loss, clinical recovery, and weight gain. No effect of the extra potassium was found on oedema loss, but some clinical

parameters appeared to improve (i.e. sepsis, cough, dyspnoea and nosocomial skin infection). Weight gain was not reported.

Early deaths (within 0–5 days of admission) were similar in both groups (11 deaths occurred in the intervention group versus 10 in the placebo group), but late deaths were significantly different (three in the intervention group versus 13 in the placebo group, $P = 0.02$). The authors acknowledged that the mortality outcome was unexpected and could have occurred by chance.

Discussants recognized the difficulties in generalizing the results of studies carried out in locations where facilities for care were limited and not all elements of the guidelines had been followed as recommended. Where this applied it would be important to replicate the findings in other locations to substantiate their generalizability. Only then would it be appropriate to consider such findings in formulating general guidelines.

Maize, the staple food in Malawi, is low in potassium and studies in locations where maize is not the staple were also suggested. In terms of practical application, not all places have access to potassium chloride or CMV and it was suggested that crushed slow-release potassium tablets are a feasible alternative (e.g. 1/2 tablet/kg/day Slow K®). Ideally the source of potassium should be added during preparation of the feeds so that the ratio of potassium to other nutrients is fixed. Slow-release tablets, however, do not dissolve readily and are therefore administered separately. Analytical grade potassium chloride, although not sold for human consumption, is available in some countries and is of sufficient purity. This can be used by making a 10% stock solution (100 g potassium chloride in 1 L water) and including 22.5 ml of this solution per litre of F75, F100 and ReSoMal (2).

Phosphorus. Little is known about phosphorus metabolism in children with severe malnutrition or about the prevalence of deficiency. The paper reviewed (20) described a retrospective, descriptive study in Malawi, which found an association between

low serum phosphate in oedematous children and mortality. Of the 68 children studied, only 57% had a normal phosphate level on admission. During treatment, approximately half received a low-phosphate diet based on egg white.

F75 provides about 1.16 mmol P/kg/day which does not meet the phosphorus requirement of 2 mmol/kg/day. F100 provides approximately 4 mmol P/kg/day. Although there is concern about the effects of providing oral phosphate supplements to severely malnourished children (e.g. diarrhoea and profound diuresis), there is a need to determine whether additional dietary phosphate can be used to normalize biochemical measures and improve outcome. Dietary phospholipids were suggested as a possible way forward.

Cysteine. Cysteine is a sulphur amino acid and component of glutathione. Reduced glutathione (GSH) is an important antioxidant and oedematous children have lower concentrations of GSH than non-oedematous children. In Jamaica, 16 oedematous children were randomly assigned to receive either cysteine (0.5 mmol/kg/day as *N*-acetylcysteine) or alanine (control) in a double-blind trial (21). Supplementation increased GSH synthesis 5-fold and resulted in more rapid loss of oedema (9 versus 14 days, $P < 0.05$).

In a separate study, cysteine supplementation of HIV-infected patients similarly improved GSH synthesis as well as natural killer cell activity and T-cell proliferation, which suggests that cysteine supplementation of oedematous children may not only reduce oxidative damage, but also improve immune function.

Discussion centred around the role of cysteine in membrane function. It was concluded that this small study showed an important metabolic effect that justifies a larger trial, which should include children with HIV. Supplementation with methionine was not considered a suitable alternative to cysteine,

as methionine utilizes glycine in the methionine-homocysteine cycle, and severely malnourished children are short of glycine.

3.6 Rehydration and ReSoMal

Severely malnourished children have excess body and intracellular sodium, even though plasma sodium may be low. The guidelines state that sodium intake should be restricted and a low-sodium oral rehydration solution (ReSoMal) is advised. Because severely malnourished children are deficient in potassium, ReSoMal contains extra potassium, as well as extra glucose or sucrose and selected minerals (and vitamins if using CMV). Although no efficacy trial of ReSoMal had been undertaken when the guidelines were written, this has now been rectified. This trial (23) was reviewed at the Consultation. It was a randomized, double-blind therapeutic trial of standard WHO-ORS (90 mmol Na/L) versus ReSoMal (45 mmol Na/L) in 130 severely malnourished children with acute watery diarrhoea in Bangladesh. Children receiving ReSoMal had a significantly better potassium status than those receiving WHO-ORS and hypokalaemia was corrected by 24 h in a greater proportion of children receiving ReSoMal than in those treated with WHO-ORS (36% versus 5%, $P = 0.0006$). Fewer children developed overhydration in the ReSoMal group (5% versus 12%), but the difference was not significant. Three children in the ReSoMal group developed severe hyponatraemia, one of whom (with a high purging rate of 18 g/kg/h) developed convulsions. The authors suggested that increasing ReSoMal to 75 mmol Na/L may be preferable.

The possibility was raised as to whether the child who developed convulsions might have had water intoxication (528 ml/kg of ReSoMal during the first 24 h). It was also suggested that there may be a case for rehydrating oedematous children differently from those with marasmus, as they handle sodium and water differently. Oedematous children tend to be more sensitive to sodium and retain excess water more easily than marasmic children (although there appear to be geographical differences in

sensitivity), and it was noted that fewer than 25% of children in the Bangladesh trial were oedematous. The composition of WHO-Oral Rehydration Solution is being changed from 90 to 75 mmol Na/L. It was broadly agreed that for the time being ReSoMal should continue to be used, but further research would be helpful to determine the optimum sodium concentration in different contexts, including severely malnourished children with severe purging, as in those with cholera.

To make ReSoMal (45 mmol Na/L) from the new 75 mmol Na/L WHO-ORS, add 1.7 L of cooled boiled water to each 1-litre sachet of WHO-ORS, add 33 ml electrolyte mineral solution (or an equivalent amount of CMV) and 40 g sugar.

3.7 Modification of the standard protocol in Kinshasa

At Kimbanseke Hospital, Kinshasa, a 5-day training workshop for the treatment of severe malnutrition was conducted in October 2002. The principles of the WHO guidelines were followed, but a different approach was used to prevent excess administration of ReSoMal during rehydration. Rather than monitoring pulse and respiratory rates every hour to indicate fluid overload (increase of 5 beats and 25 breaths/min), short-term weight change, respiratory distress and increasing liver size were used. A weight-monitoring algorithm was devised to guide decisions as to whether to continue, stop or increase administration of ReSoMal. Rapid breathing plus weight gain was used to signify heart failure, whereas fast breathing with weight loss signified pneumonia. Despite being a region with a high prevalence of HIV, the case-fatality rate from October 2002–June 2003 was 20/494 (3%) in contrast to 73/415 (17%) during March–October 2002 when less attention had been given to fluid overload. In many hospitals, fluid overload resulting in heart failure is often misdiagnosed as pneumonia. This weight-monitoring approach has been scaled up in Angola, Burundi and Ethiopia, where the reported case-fatality rate is 3–6%.

3.8 Criteria for early discharge to home-based treatment

The guidelines encourage continued hospital care until recovery, but also provide criteria for early discharge to home care. One of these criteria is that children being considered for home care should be at least 12 months old. Experiences of home rehabilitation in Bangladesh were presented. After completing the initial phase of treatment, 225 severely malnourished children were randomly assigned either to continuing hospital-based care (NRU), home care with outpatient follow-up (OPD) or home care with home follow-up. Follow-up was weekly for the first month and then fortnightly until the child achieved 80% weight-for-length. Both follow-up groups received multivitamins, zinc syrup, folic acid and iron, but no food supplements were given. All children were oedema-free at the start of home care. There was one death in the NRU group from nosocomial infection. Weight gains in the NRU, OPD and home-visited groups were 11.6, 7.5 and 10.4 g/kg/d, respectively and the costs/patient of rehabilitation were US\$ 76, 21 and 22, respectively. Infants aged 6–12 months were included in the study. It was concluded that the age criterion for discharge to home care could be lowered to 6 months.

Discussion included practical problems, such as violence, that home visitors face in some settings and the difficulty of travelling around communities. Scaled up studies in other settings were suggested, although there were differing opinions as to the sustainability of home visits.

4. RESEARCH

It was recognized that nongovernmental organizations (NGOs) and United Nations (UN) agencies collect a great deal of information that could be used to advantage. Formal collaborative research between NGOs, UN agencies and academic institutions

was encouraged, so that data analyses could be ongoing, timely and have technical oversight.

Infants less than 6 months of age

- To guide policy regarding optimum dietary management of very young severely malnourished infants, there is an urgent need for observational studies and randomized trials of alternative formulations, for example a trial comparing the results of using F100 with those of using diluted F100 in the rehabilitation phase.
- For young, severely malnourished, HIV-positive infants in areas where definitive diagnostic virological testing of HIV is not available, research is needed to identify signs that are predictive of HIV.

Children living with HIV/AIDS

- To guide decisions about ARV treatment, studies of the safety of ARVs in severe malnutrition, and pharmacokinetic studies, are essential. These can be conducted on small samples of children.
- Larger scale studies are needed to determine when to start treatment with ARVs (e.g. level of immunosuppression and phase of malnutrition treatment), effective drug regimens and drug interactions (e.g. between ARVs and TB drugs). To help elucidate when to start ARVs, data will be needed regarding the effects of severe malnutrition on CD4% in HIV-infected and uninfected children of different ages.
- Prospective case-control studies are required to determine if there are important differences in the clinical response to case-management between severely malnourished children infected with HIV and those who are uninfected. Such studies may help to develop better approaches for the care of HIV-positive children with severe malnutrition. Two populations of infected children are envisaged, namely

those with symptomatic HIV and those with no symptoms whose seropositive status is discovered by routine testing.

- More studies of the performance of the malnutrition guidelines (e.g. on speed of recovery and the case-fatality rate) in areas of high HIV prevalence are needed.
- Postmortem studies in different settings will help define common pathological profiles.
- Interrupting perinatal transmission of HIV to children was seen both as a programmatic imperative that must be scaled up for adequate coverage and also as a research imperative.
- Randomized trials to determine optimum micronutrient intakes for HIV-exposed and HIV-infected children with severe malnutrition were suggested.

Pathophysiology

Research was proposed on the following:

- renal handling of sodium in severely malnourished children, with and without HIV, and the effect of prophylactic cotrimoxazole on renal tubule function;
- supplementation with potassium, phosphate, cysteine and vitamin A to determine optimum dosages; and
- lactose-free feeds.

Rehydration

- Now that the new WHO-ORS (75 mmol Na/L) is available, a randomized double-blind trial was suggested to determine the optimum sodium concentration of ReSoMal (e.g. comparing 75 versus 45 versus 37.5 mmol Na/L).

Early discharge to home rehabilitation

- Operational research is needed to identify feasible ways of safely providing multi-micronutrients to children at home.

- Cost-effectiveness studies of alternative home-based and community-based approaches in different settings were proposed, including comparisons of home-prepared foods and RUTF.

Implementation of the guidelines

- Studies are required to identify factors that constrain or promote implementation of the guidelines in different settings.
- Identification of priority actions that might simplify treatment and assist in monitoring implementation of the guidelines and promote quality assurance was proposed.

Training programmes

- Operational research to evaluate the effectiveness of training programmes is needed.
- Trials of different approaches to training are also needed to determine the most cost-effective way(s) to change case-management practices. These may include interventions to change attitudes and improve motivation.

5. CONCLUSIONS

The WHO guidelines have played a valuable role in establishing a base of improved practice in the management of severely malnourished children. When the guidelines are followed, they effectively lead to a substantial reduction in child deaths, but current coverage is poor worldwide and there are a number of important issues that need to be addressed if the guidelines are to be rolled out effectively to help achieve the Millennium Development Goal of improved child survival. One of the urgent goals is the incorporation of the guidelines into medical and nursing curricula, and into in-service training programmes. Paediatric textbooks need to be updated in line with the guidelines. In many countries, weaknesses in local and central health systems, staff shortages and resource constraints limit

effective delivery and sustainability of the measures in the guidelines and these problems need to be addressed.

Gaps in knowledge remain, particularly in relation to feeding very young infants and to caring for children living with HIV/AIDS. Research is needed to guide decisions about optimum dietary management for infants aged < 6 months. As yet there are no published studies of the effectiveness of antiretroviral therapy in severely malnourished children who are HIV-positive and information is needed on the pharmacodynamics of different drugs and regimens. The level of immunosuppression and the phase of malnutrition treatment at which to start antiretroviral therapy also need to be determined. Nutritional supplementation may have an important impact on the progression of HIV disease, especially when combined with effective antiretroviral treatment. When new information becomes available and the strength of the evidence is assessed, aspects of the guidelines may need to be revised. The revised guidelines should then be made widely available as quickly as possible, utilizing suitable methods of dissemination such as web-based communication.

Evidence was considered for possible improvements in practice regarding fluid and electrolyte homeostasis, and the effective provision of potassium, phosphate, vitamin A, cysteine and oral rehydration solution. Each of these areas was recognized as being of importance, but current evidence was not sufficiently strong to support a change in practice. Focused research commissioned to address specific issues was recommended to achieve a clearer understanding of optimum case-management. On the assumption that this research is carried out, it might be anticipated that a major review of the guidelines would be needed in the future. The year 2010 was suggested as a reasonable target for completion of this task.

The Consultation has served to emphasize the importance of having a formal mechanism through which a reliable evidence-

base, suitable for guiding policy, could be generated, and through which future advances in understanding might be incorporated into guidelines in a timely way. Currently such a mechanism does not exist and the Consultation considered that the creation of a group, such as a Technical Advisory Group, would be of value, as would closer ties between those engaged in cutting-edge HIV research and those with expertise in severe malnutrition.

The next steps will be:

- a wider meeting with key partners to share the conclusions of this Consultation with a view to consolidating implementation of the WHO guidelines and broadening the research base;
- a planning meeting to consider the remit, structure and potential value of a Technical Advisory Group, and the logistics of establishing a web-based information forum; and
- preparation of an additional module for the WHO Training Course on Improving Treatment of Severe Malnutrition. This module would focus on the treatment of severely malnourished children living with HIV/AIDS and would include the programmatic changes highlighted in this report.

References

1. *Management of severe malnutrition: a manual for physicians and other senior health workers*. Geneva, World Health Organization, 1999.
2. *Management of the child with a serious infection or severe malnutrition: guidelines for care at the first-referral level in developing countries*. Geneva, World Health Organization, 2000.
3. Ashworth A et al. WHO guidelines for management of severe malnutrition in rural South African hospitals: effect on case fatality and the influence of operational factors. *Lancet*, 2004, 363:1110–1115.
4. Deen JL et al. Implementation of WHO guidelines on management of severe malnutrition in hospitals in Africa. *Bulletin of the World Health Organization*, 2003, 81: 237–243.
5. Life Sciences Research Office. *Assessment of nutrient requirements for infant formulas*. Prepared for Center for Food Safety and Applied Nutrition, Food and Drug Administration., Bethesda, MD, American Society for Nutritional Sciences, 1998. pp 75–76.
6. Fomon SJ, Ziegler EE. Renal solute load and *potential* renal solute load in infancy. *Journal of Pediatrics*, 1999, 134:11–14.
7. *Pregnancy, childbirth, postpartum and newborn care. A guide for essential practice*. Geneva, World Health Organization, 2003.
8. *Managing newborn problems. A guide for doctors, nurses and midwives*. Geneva, World Health Organization, 2003.
9. Chintu C et al. Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind, randomised placebo-controlled trial. *Lancet*, 2004, 364:1865–1869.
10. *Treatment of tuberculosis: guidelines for national programmes*. Geneva, World Health Organization, 2003.

11. Molyneux E. Bacterial infections in children with HIV/AIDS. *Tropical Doctor*, 2004, 34:195–198.
12. Jiamton S et al. A randomized trial of the impact of multiple micronutrient supplementation on mortality among HIV-infected individuals living in Bangkok. *AIDS*, 2003, 17:2461–2469.
13. Fawzi WW et al. A randomized trial of multivitamin supplements and HIV disease progression and mortality. *New England Journal of Medicine*, 2004, 351:23–32.
14. Coutoudis A et al. The effects of vitamin A supplementation on the morbidity of children born to HIV-infected women. *American Journal of Public Health*, 1995, 85:1076–1081.
15. Fawzi WW et al. A randomised trial of vitamin A supplements in relation to mortality among HIV infected and uninfected children in Tanzania. *Pediatric Infectious Disease Journal*, 1999, 18:127–133.
16. Donnen P et al. Randomized placebo-controlled clinical trial of the effect of a single high dose or daily low doses of vitamin A on the morbidity of hospitalized, malnourished children. *American Journal of Clinical Nutrition*, 1998, 68:1254–1260.
17. Sylla A, N'diaye O, Diouf S, Fall CS, Diouf M et al. A double blind comparative trial of the effect of single high-dose versus daily low dose vitamin A on prolonged diarrhoea in Senegal. *Archives de Pediatre*, 2002, 9:975.
18. Donnen P et al. Daily low doses of vitamin A compared with single high dose improves survival of malnourished children in Senegal. XX1 International Vitamin A Consultative Group (IVACG) meeting. 2003. Abstract T15p56.
19. Manary MJ, Brewster DR. Potassium supplementation in kwashiorkor. *Journal of Pediatric Gastroenterology and Nutrition*, 1997, 24:184–201.
20. Manary MJ, Hart CA, Whyte MP. Severe hypophosphatemia in children with kwashiorkor is associated with increased mortality. *Journal of Pediatrics*, 1998, 133:789–791.

21. Badaloo A et al. Cysteine supplementation improves the erythrocyte glutathione synthesis rate in children with severe edematous malnutrition. *American Journal of Clinical Nutrition*, 2002, 76:646–652.
22. Jackson AA. Glutathione in kwashiorkor. *American Journal of Clinical Nutrition*, 2002, 76:495–496.
23. Alam NH et al. Efficacy and safety of a modified oral rehydration solution (ReSoMal) in the treatment of severely malnourished children with watery diarrhea. *Journal of Pediatrics*, 2003, 143:614–619.



ANNEX 1
WORLD HEALTH ORGANIZATION

**Informal Consultation to Review Current Literature on
Management of Severe Malnutrition in Hospitals,
Geneva, Switzerland, 6–7 September 2004
Salle G**

AGENDA

6 September 2004

09:00–09:30	Welcoming remarks Introduction of participants Nomination of Chairperson and Rapporteur Adoption of agenda and programme
09:30–10:30	Introduction of the topics to review Professor Alan Jackson Dr Sultana Khanum Discussion
10:30–10:45	<i>Coffee/tea break</i>
10:45–11:30	Professor Alan Jackson: Are different guidelines for infants < 6 months required?
11:30–12:30	Discussion
12:30–14:00	<i>Lunch</i>

14:00–14:15	Dr Nigel Rollins: Are the feeding/micronutrient guidelines appropriate for children with (i) asymptomatic HIV, or (ii) AIDS, or (iii) unknown HIV status in high HIV prevalence areas?
14:15–14:30	Dr James Bunn: Are the guidelines for management of HIV–related infections appropriate?
14:30–14:45	Dr Gareth Tudor-Williams: Should ARVs be part of hospital treatment?
14:45–15:30	Discussion
15:30–15:45	<i>Coffee/tea break</i>
15:45–16:00	Professor Michael Golden: Should the dose of vitamin A be reduced for (i) all children (ii) oedematous children? (Review of the evidence.)
16:00–16:30	Discussion
16:30–16:45	Professor Michael Krawinkel: Should the dose of potassium be increased? (Review of the evidence.)
16:45–17:00	Discussion
17:00–17:15	Professor David Brewster: Should extra phosphorus be prescribed? If so, how? (Review of the evidence.)
17:15–17:30	Discussion

7 September 2004

09:00–09:15	Professor Alan Jackson: Should cysteine be prescribed? (Review of the evidence.)
09:15–09:30	Discussion
09:30–09:45	Dr Geert Tom Heikens: Do the guidelines re ReSoMal need changing? (Review of the evidence.)
09:45–10:00	Discussion
10:00–10:15	Professor Michael Golden: Modification of the standard protocol in Kinshasa and effect on mortality.
10:15–10:30	Discussion
10:30–10:45	<i>Coffee/tea break</i>
10:45–11:00	Dr Tahmeed Ahmed: Should the criteria for early discharge to home-based treatment be relaxed?
11:00–11:30	Discussion
11:30–12:30	Research agenda
12:30–14:00	<i>Lunch</i>
14:00–14:30	Research agenda (continued)
14:30–15:00	Professor Ann Ashworth: Summary and final recommendations
15:00–15:30	Discussion

<i>15:30–15:45</i>	<i>Coffee/tea break</i>
15:45–16:30	Next steps
16:30–	Conclusions and wrap-up



WORLD HEALTH ORGANIZATION

**Informal Consultation to Review Current Literature on
Management of Severe Malnutrition in Hospitals,
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Salle G**

LIST OF PARTICIPANTS

Temporary Advisers

Dr Tahmeed Ahmed
International Centre for Diarrhoeal
Diseases Research, Bangladesh
Mohakhali
Dhaka 1212
Bangladesh

Tel. : +880 2 8811751-60/
ext. 2304
+880 2 8812353-57/
ext. 2304
Office direct : 988 2399
Fax : +880 2 882
3116/6050
Email :
tahmeed@icddrb.org

Professor Ann Ashworth
Nutrition & Public Health Intervention
Research Unit
Department of Epidemiology and Population Health
London School of Hygiene and Tropical Medicine
Keppel Street
London WC1E 7HT
England

Tel. : +44 20 7958 8101
Fax: + 44 20 7958 8101
Email :
ann.hill@lshtm.ac.uk

Professor David Brewster
Clinical Dean
NT Clinical School (Flinders University)
PO Box 41326
Casuarina, NT 0811
Australia

Tel. : +61 8 8922 8118
Fax : +61 8 8922 7928
Email:
david.brewster@edu.au

Dr James Bunn
Senior Lecturer and
Honorary Consultant Paediatrician
Tropical Child and Reproductive Health Group
Liverpool School of Tropical Medicine
Pembroke Place
Liverpool L3 5QA
England

Tel. : +44 151 705 3205
Fax : +44 151 705 3329
Email :
jegbunn@liverpool.ac.uk

Dr Bruce Cogill
Project Director
Food and Nutrition Technical Assistance Project
(FANTA)
USAID/AED
1825 Connecticut Avenue, NW
AED Suite 800
Washington, DC 20009-5271
USA

Tel. : +1 202 884 8722
Fax : +1 202 884 8432
Email :
bcogill@aed.org

Professor Michael Golden
Pollgorm, Ardbane
Downings, Letterkenny
Co Donegal
Ireland

Tel. : +353 74 91 55 164
Fax :
Email :
mike@pollgorm.net

Dr Geert Tom Heikens
Visiting Senior Lecturer Tropical Child Health
University of Amsterdam
Consultant Paediatrician
Gelre Hospitals
POBox 9014
7300 DS Apeldorn
Netherlands

Tel. : +31 55 355 1716
Fax : +31 55 55 11 687
Email :
gt.heikens@gelre.nl
Email 2 :
GEERTTOM@Heikens.org

Professor Alan Jackson
Director
Institute of Human Nutrition
Southampton General Hospital (MP 113)
remona Road
Southampton SO16 6YD
England

Tel. : +44 23 8079 6317
Fax : +44 23 8079 4945
Email :
A.A.Jackson@soton.ac.uk

Professor Michael Krawinkel
International Nutrition and Pediatrics
Institute of Nutritional Sciences
Wilhelmstrasse 20
D-35392 Giessen
Germany

Tel. : +49 641 993 9048
Fax.: +49 641 993 9039
Email
Michael. Krawinkel@
ernaehrung.uni-giessen.de

Professor Nigel Rollins
Head of Maternal and Child Health
Department of Paediatrics and Child Health
Nelson R. Mandela School of Medicine
University of Kwazulu-Natal
Private Bag 7
Congella 4013
South Africa

Tel. : +27 31 260 4352
Fax : +27 31 260 4388
Email :
rollins@ukzn.ac.za

Dr Gareth Tudor Williams
Chairman
Children's HIV Association for the UK and Ireland
(CHIVA)
Senior Lecturer in Paediatric Infectious Diseases
Department of Paediatrics
St. Mary's Hospital
London W2 1NY
England

Tel.: +44 20 7886 6349
/6304
Fax : +44 20 7886 6341
Email : g.tudor-williams
@imperial.ac.uk

Mrs Susie Villeneuve
Project Officer
Nutrition in Emergencies
United Nations Children's Fund
3, United Nations Plaza
New York, NY 10017
USA

Tel. : +1 212 326 7377
Fax :
Mobile : +1 917 257 9726
Email :
svilleneuve@unicef.org

Observer

Dr Claudine Prudhon
United Nations System
Standing Committee on Nutrition
c/o World Health Organization
20, Avenue Appia
CH-1211 Geneva 27
Switzerland

Tel. : +41 22 791 34 81
Fax : +41 22 798 88 91
Email :
prudhonc@who.int
scn@who.int

World Health Organization

Dr Sultana Khanum
Consultation Coordinator
Nutrition for Health and Development (NMH/NHD) Email: khanums@who.int

Tel. : +41 22 791 2624
Fax : +41 22 791 4156

Mrs Randa Saadeh
Scientist
Nutrition for Health and Development NMH/NHD) Email : saadehr@who.int

Tel. : +41 22 791 3315
Fax : +41 22 791 4156

Mrs Zita Weise Prinzo
Technical Officer
Nutrition for Health and Development (NMH/NHD) Email :
weiseprinzo@who.int

Tel. : +41 22 791 4440
Fax : +41 22 791 4156

Dr André Briend
Medical Officer
Child and Adolescent Health and Development
(FCH/CAH)

Tel. : +41 22 791 1447
Fax : +41 22 791 4853
Email :
brienda@who.int

Dr Martin Weber
Medical Officer
Child and Adolescent Health and Development
(FCH/CAH)

Tel. : +41 22 791 2603
Fax : +41 22 791 4853
Email : weberm@who.int

Dr Siobhan Crowley
Medical Officer
Noncommunicable Disease Prevention
and Health Promotion
(HTM/HIV/PRV)

Tel. : +41 22 791 1609
Fax : +41 22 791 4834
Email : crowleys@who.int

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For further information please contact:

Dr Sultana Khanum
Department of Nutrition for Health and Development
World Health Organization
20 Avenue Appia
1211 Geneva 27, Switzerland
Telephone: +41 22 791 26 24
Fax: +41 22 791 41 56
Email: khanums@who.int
Website: www.who.int/nut