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Treatment of severe and moderate acute malnutrition in low- and middle-income settings: a systematic review, meta-analysis and Delphi process

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B **:** Globally, moderate acute malnutrition (MAM) and severe acute malnutrition (SAM) affect approximately 52 million children under five. This systematic review evaluates the effectiveness of interventions for SAM including the World Health Organization (WHO) protocol for inpatient management and community-based management with ready-to-use-therapeutic food (RUTF), as well as interventions for MAM in children under five years in low- and middle-income countries.

: We systematically searched the literature and included 14 studies in the meta-analysis. Study quality was assessed using CHERG adaptation of GRADE criteria. A Delphi process was undertaken to complement the systematic review in estimating case fatality and recovery rates that were necessary for modelling in the Lives Saved Tool (LiST).

: Case fatality rates for inpatient treatment of SAM using the WHO protocol ranged from 3.4% to 35%. For community-based treatment of SAM, children given RUTF were 51% more likely to achieve nutritional recovery than the standard care group. For the treatment of MAM, children in the RUSF group were significantly more likely to recover and less likely to be non-responders than in the CSB group. In both meta-analyses, weight gain in the intervention group was higher, and although statistically significant, these differences were small. Overall limitations in our analysis include considerable heterogeneity in many outcomes and an inability to evaluate intervention effects separate from commodity effect. The Delphi process indicated that adherence to standardized protocols for the treatment of SAM and MAM should have a marked positive impact on mortality and recovery rates; yet, true consensus was not achieved.

C **:** Gaps in our ability to estimate effectiveness of overall treatment approaches for SAM and MAM persist. In addition to further impact studies conducted in a wider range of settings, more high quality program evaluations need to be conducted and the results disseminated.

Globally, approximately 33 million children under five years of age are affected by moderate acute malnutrition (MAM), defined as a weight-for-height z-score (WHZ) between -2 and -3, and at least 19 million children under five by severe acute malnutrition (SAM), defined as a WHZ of <-3 [1,2]. For children with SAM, the risk of death is approximately 10-fold higher compared to children with a z-score ≥ – 1 [3]. Based on an analysis by UNICEF, WHO and the World Bank [2], 32 of 134 countries for which there was data on prevalence of acute malnutrition (WHZ <-2) had a prevalence of 10% or more – a threshold that represents a "public health emergency requiring immediate intervention" [2]. This analysis also showed that, since 1990, prevalence rates of wasting (acute malnutrition, WHZ <-2) have declined

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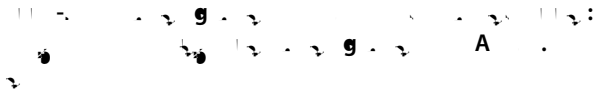
three times more slowly than for stunting (chronic malnutrition, height-for-age z-score <-2), decreasing by 11% and 35% respectively.

asterisk next to the authors' names in the forest plots indicates the use of unpublished data.

We coded and categorized the types of interventions in each article. For moderate acute malnutrition, we conducted a meta-analysis only on ready-to-use-supplementary food (RUSF) compared with CSB, as this was the only comparison with multiple studies that could be pooled. Likewise, for severe acute malnutrition, we con-

2.20) (figure 3). There was substantial heterogeneity (I^2 = 92%), the effect was only marginally statistically significant, and this outcome was graded as low quality (see table 1 for



A literature review by Schofield and Ashworth [24] indi-

adequately describe the intervention (see additional file 3 for study assessment).

None of the studies provided sufficient information to ensure that each step of the WHO protocol was followed and many noted variations from the protocol. One study [31,32] excluded children with severe complications and thus may not be generalizable. Case fatality rates ranged from 3.4% to 35% (see table 2). The highest CFR

a hospital [29]. Two additional observational studies documented that implementing changes to dietary and clinical management did not seem to be sufficient to promote substantial reductions in case fatality rates. Key factors associated with improved outcomes were related to quality of care and institutional culture, including staff morale, attentiveness of nurses and support structures at the managerial level [36,37].

Comparison of RUSF and CSB

Our review identified five studies investigating the effect of Ready-to-Use Supplementary Food (RUSF) compared to Corn Soy Blend (CSB) in moderately malnourished children under five years of age [38-42]. Two of the studies were cluster randomized controlled trials (cRCTs), one set in 10 health centres and health posts in the Sidama zone of Ethiopia [39] and the other in the Dioila health district in Mali [38]. Three of the studies were randomized controlled trials (RCTs). Two were located in southern Malawi [40,41], and one in the Zinder region of southern Niger [42]. Two studies took place from 2007 to 2008 [38,42]; the remaining three studies took place during 2009 and 2010 [39-41]. We assessed the quality of the studies to be low [42], moderate [38], moderate/high [39,40] and h

There was no significant difference in mortality between home-based or inpatient care (figure 9). However, the stu-

recovery between the two antibiotic arms. Rates of weight gain among children who recovered were higher in the antibiotic arms compared to the placebo arm. HIV status was not known for over half of the children in the study. Additional studies are needed to strengthen the evidence base on whether children with uncompli-

by context, due to the limited number of trials available, the lack of detail given on the interventions and analysis in many studies, and the requirement for a single effect estimate in LiST.

Further to the issues inherent in the analysis, there are issues with individual studies that warrant discussion. The diets given to children were often not described in detail, and the amounts of CSB given to the comparison group varied, sometimes including enough to share with family members. Thus dietary intake of study participants is not clear in all cases. Furthermore, all but one of the studies in the meta-analysis were conducted in Africa, with a bias towards Malawi (see additional file 2), thus limiting the generalizability of the results. Additionally, all studies passively recruited participants who were brought to treatment facilities. This may introduce bias if there are systematic differences between caregivers who are more likely, and those who are less likely, to bring their children to facilities for treatment.

Our review was unable to utilize a substantial proportion of studies due to inconsistencies in admission criteria, variability in the definition of acute malnutrition (including the use of weight-for-age to assess nutritional status), and irregularities in how data is reported. In order to strengthen our understanding of the effectiveness of interventions, through the use of meta-analysis, there should be standard case definitions and reporting of outcomes at standardized time intervals. Admission criteria should be based on the WHO definition of acute malnutrition, or children meeting these criteria should be presented in a disaggregated analysis.

Further high quality impact studies of approaches to managing SAM and MAM are needed. Particularly studies that reflect a broader range of settings where these conditions are prevalent, including a range of geographic locations and areas with different disease prevalence (i.e. HIV). Though this area of research can present challenges for intervention studies, there are study design options and data analysis techniques that allow for high quality research. Where randomized controlled trials are not feasible, another option would be to employ a stepped-wedge design for research on community-based management of SAM or MAM.

Our meta-analysis was constrained with respect to the types of outcomes we were able to pool. Length of stay, relapse (requiring re-admission to the hospital), default rate, sustained recovery and cost-effectiveness were not routinely measured, but are essential factors to consider in program planning. Furthermore, all but one of the studies included in this review follow children for a relatively short period of time, providing little insight into long-term effects. A recent follow-up study by Chang et al. [66] found significant differences in sustained recovery over 12-months of follow-up, depending on the treatment given. Of all children successfully treated for MAM, sustained recovery was significantly more likely in those treated with soy/whey RUSF compared to those treated with either soy RUSF or CSB++; however, the authors concluded that all children in the study remained vulnerable. More follow-up studies are needed to illuminate long-term effects on developmental outcomes, stunting, and the transition back to a home diet. Standardized follow-up intervals over a longer time period, and reporting on a wider range of outcomes would allow for higher quality meta-analyses and a more robust understanding the intervention effects.

Similarly, trials are needed to compare different approaches for the management of MAM that consider local context, as a one-size-fits all approach is not appropriate [67]. While food supplementation is necessary in humanitarian emergencies and chronic food insecurity, acute malnutrition is not confined to situations of conflict or famine [68]. In relatively more stable situations, further research is needed on preventive approaches that address upstream determinants of acute malnutrition, illustrated by the range of ideas brought forth in the Delphi exercise (see additional file 4).

As the body of literature grows, it will also be important to disaggregate meta-analyses according to context. Therefore, greater geographic representation is needed, as are studies designed to explore the impact of factors that likely affect the individuals' treatment outcomes, such as HIV status and household food insecurity, as well as studies that are designed to tease out the elements of successful programs, beyond the choice of commodity.

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The paradigm shift towards community-based treatment of SAM has transformed the approach to treating acute malnutrition. Community-based treatment is backed by substantive programmatic evidence; however, there are clear gaps in the availability of well-designed studies evaluating the effectiveness of interventions to manage SAM and MAM in a range of contexts. Thus, establishing effect estimates for LiST proved challenging. The meta-analysis demonstrates some positive effects of the use of RUTF in comparison to CSB for the treatment of SAM or MAM in the community; yet, the effects were generally small and several outcomes had substantial heterogeneity. Meanwhile, the results of the Delphi indicate that the use of standardized protocols for treating complicated SAM, uncomplicated SAM, and MAM, should lead to low mortality and high recovery rates. To close the gap between research and practice, further studies are needed that compare approaches to managing SAM and MAM, taking local context into consideration.

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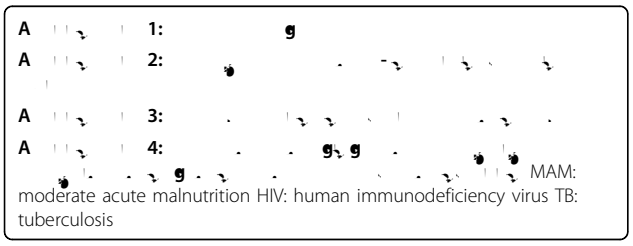

MAM: moderate acute malnutrition HIV: human immunodeficiency virus TB: tuberculosis

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The authors declare that they have no competing interests.

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LML and ZAB conceptualized the review and analysis. LML led the systematic review and Delphi process and wrote the manuscript with substantial inputs from PW and ZAB. KW was involved in abstraction, analysis, Delphi and writing the first manuscript draft. PW and TA significantly contributed throughout the stages of the review and manuscript preparation.

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