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Since publication of their article, the authors report no further potential conflict of interest.

1. Lansberg MG, Straka M, Kemp S, et al. MRI profile and

response to endovascular reperfusion after stroke (DEFUSE 2): a prospective cohort study. Lancet Neurol 2012;11:860-7.

- 2. Parsons M, Spratt N, Bivard A, et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. N Engl J Med 2012;366:1099-107.
- **3.** Davis SM, Donnan GA, Parsons MW, et al. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. Lancet Neurol 2008;7:299-309.
- **4.** Albers GW, Thijs VN, Wechsler L, et al. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) study. Ann Neurol 2006;60: 508-17.

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Antibiotics for Uncomplicated Severe Malnutrition

TO THE EDITOR: Trehan et al. (Jan. 31 issue)1 found that amoxicillin or cefdinir improved recovery from severe malnutrition among children in Malawi. The hypothesized reasons for their effectiveness include an underlying immunodeficiency related to malnutrition.1,2 However, although a major cause of immunodeficiency in Malawi is the human immunodeficiency virus (HIV), 68% of enrolled children were not tested for HIV; among those tested, 22% had HIV infection. Children known to be infected with HIV had the highest risk of treatment failure or death. Malnutrition is a well-known condition in children with HIV disease; outpatient therapeutic programs are important venues for the identification of infected children.3 Unfortunately, incomplete ascertainment of HIV status and inadequate management of infection in children, including trimethoprim-sulfamethoxazole prophylaxis, antiretroviral therapy (ART), or both, may confound the interpretation of the trial findings. The proper management of HIV infection could modify the effect of amoxicillin and cefdinir, and ART can improve weight gain and be lifesaving in infected children.2 Offering HIV testing (and referral for HIV care for those infected) is an internationally accepted practice in clinical trials and is consistent with Malawi's national HIV testing and treatment guidelines.^{3,4} It would, therefore, be helpful to know why testing was not performed.

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The views expressed in this letter are those of the authors and do not necessarily represent the official position of the CDC or the Agency for Toxic Substances and Disease Registry.

No potential conflict of interest relevant to this letter was reported.

- 1. Trehan I, Goldbach HS, LaGrone LN, et al. Antibiotics as part of the management of severe acute malnutrition. N Engl J Med 2013;368:425-35.
- 2. Antiretroviral therapy for HIV infection in infants and children: toward universal access. 2010 revision. Geneva: World Health Organization (http://www.who.int/hiv/pub/paediatric/infants2010/en/index.html).
- 3. Malawi Ministry of Health. Guidelines for pediatric HIV testing and counseling. 2007 (http://www.ilo.org/wcmsp5/groups/public/---ed_protect/---protrav/---ilo_aids/documents/legaldocument/wcms_151227.pdf).
- **4.** *Idem.* Treatment of AIDS: guidelines for the use of antiretroviral therapy in Malawi. 3rd ed. April 2008 (http://apps.who.int/medicinedocs/documents/s18803en/s18188en.pdf).

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TO THE EDITOR: Trehan et al. concluded that antibiotics should be used routinely with ready-to-use therapeutic food (RUTF) for severe malnutrition in outpatients, irrespective of concomitant infectious disease. Augmentation of RUTF is sorely needed, but we question the magnitude of the benefit and suggest that it be weighed against alternative interventions and the likely costs of increased antibiotic resistance.

The researchers reported that adding a 7-day antibiotic course to RUTFs resulted in significant reductions in mortality and increases in recovery rates. Careful analysis of the findings, however, shows that among survivors, the differential in the rate of treatment failure between the antibiotic treatment groups and the placebo group was less than 1%. In addition, the study fails to take into account infections, breast-feeding, and status with regard to HIV and AIDS.

Given the high prevalence of moderate and re-

lapsing child malnutrition combined with the unregulated use of antibiotics in some settings,^{2,3} the authors' suggestion will probably lead to broad, repeated antimicrobial therapy and increased selective pressure. Short-term, marginal savings will be counterproductive if deaths due to complications induced by resistant bacteria rise. Furthermore, a recent meta-analysis showed weak evidence to support the current recommendation from the World Health Organization to routinely include antibiotics as part of the treatment of pediatric outpatients with severe acute malnutrition in the absence of obvious clinical infectious illnesses.⁴

We do not suggest changes in the current practice of augmenting RUTFs with antibiotics for the treatment of severe malnutrition in supervised settings. However, the extension of this practice into the community requires an assessment of the likely costs — in lives — of increasing selective pressure for antibiotic resistance. We support further research and the immediate expansion of validated interventions, including breast-feeding, the use of probiotics, and increased access to traditional RUTFs and clean water. These strategies will be more effective in reducing malnutrition in the long run.

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- 1. Ciliberto MA, Sandige H, Ndekha MJ, et al. Comparison of home-based therapy with ready-to-use therapeutic food with standard therapy in the treatment of malnourished Malawian children: a controlled, clinical effectiveness trial. Am J Clin Nutr 2005;81:864-70.
- 2. Haak H, Hardon A. Indigenised pharmaceuticals in developing countries: widely used, widely neglected. Lancet 1988;2: 620-1.
- **3.** Chang CY, Trehan I, Wang RJ, et al. Children successfully treated for moderate acute malnutrition remain at risk for malnutrition and death in the subsequent year after recovery. J Nutr 2013;143:215-20.
- **4.** Alcoba G, Kerac M, Breysse S, et al. Do children with uncomplicated severe acute malnutrition need antibiotics? A systematic review and meta-analysis. PLoS One 2013;8(1):e53184.

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TO THE EDITOR: In their study in Malawi, Trehan et al. found that adding a 1-week course of antibiotics to an outpatient therapeutic feeding program for severely malnourished children decreased mortality. Since 35% of deaths among young children globally have been attributed to undernutrition, such findings are welcome.¹

Trehan et al. also show that the risk of death in this population continues beyond the initial week of therapy, suggesting that longer-term solutions are needed. Given the environment in which these children live, we suspect that they are frequently exposed to contaminated drinking water. The incidence of diarrhea and pneumonia, diseases that the authors speculate were modulated by antibiotics, can be reduced by good hand-washing practices and the treatment of drinking water by 31% and 21%, respectively — or more.^{2,3}

In addition, interventions to improve hygiene and water quality do not induce antimicrobial resistance, and their effects are not reduced in the presence of drug-resistant microbes. Promoting the use of safe drinking water, soap, and good hygiene in outpatient therapeutic feeding protocols may help to protect these vulnerable children over a longer period, while also benefiting their siblings and other household members.

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- **1.** Black RE, Allen LH, Bhutta ZA, et al. Maternal and child undernutrition: global and regional exposures and health consequences. Lancet 2008;371:243-60.
- **2.** Aiello AE, Coulborn RM, Perez V, Larson EL. Effect of hand hygiene on infectious disease risk in the community setting: a meta-analysis. Am J Public Health 2008;98:1372-81.
- **3.** Fewtrell L, Kaufmann RB, Kay D, Enanoria W, Haller L, Colford JM Jr. Water, sanitation, and hygiene interventions to reduce diarrhoea in less developed countries: a systematic review and meta-analysis. Lancet Infect Dis 2005;5:42-52.

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THE AUTHORS REPLY: We agree wholeheartedly with Koumans et al. that the integration of HIV services into the care of children with severe acute malnutrition is essential to improving our ability to address their overall health care needs.

We also agree that untreated HIV infection is probably a confounder in the recovery of children with severe acute malnutrition. For the purposes of our study, we did not perform universal testing of enrolled children for HIV in order to replicate real-world practices in rural health centers in Malawi. At these centers, trained HIV counselors and rapid HIV-antibody test kits are often not available, and the stigma associated with HIV testing often scares caregivers away from bringing their malnourished children to health centers for care. We therefore chose not to conduct universal testing for HIV but instead asked about previous testing at the time of study enrollment and then privately encouraged testing only for those children who were not recovering promptly, a practice that would be part of usual care in this setting.

We disagree with the sentiment expressed by Okeke et al. that the risk of antibiotic resistance outweighs the key benefit seen in this study — a 40% reduction in mortality from a disease that affects at least 20 million children annually. Although we certainly do not wish to contribute to the growing plague of antibiotic resistance, it is difficult to ignore the potentially lifesaving benefit proffered by this affordable and readily available adjunct to current therapy; meanwhile, the promotion of breast-feeding and improved sanitation should certainly be pursued simultaneously, as Bowen and Tauxe suggest.

The approaches to diagnosis and therapy tested in this study — syndromic, simple, and standardized — are suited to the strategy of integrated community case management,² which has already been effective in the treatment of other common childhood illnesses when implemented by community health workers. In contrast with the assertion by Okeke et al., a high relapse rate has

not been reported after the successful treatment of severe acute malnutrition,³ probiotics have not proved to be of significant benefit in this context,⁴ and the study they cite by Alcoba et. al, which was conducted before our trial, specifically suggests that a randomized, controlled trial is needed to definitively answer the question about the need for antibiotics as part of the management of severe malnutrition.⁵ We agree that our results should not be extrapolated to those with moderate malnutrition and that our findings should be implemented judiciously.

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- 1. Trehan I, O'Hare BA, Phiri A, Heikens GT. Challenges in the management of HIV-infected malnourished children in sub-Saharan Africa. AIDS Res Treat 2012;2012:790786.
- 2. Marsh DR, Hamer DH, Pagnoni F, Peterson S. Introduction to a special supplement: evidence for the implementation, effects, and impact of the integrated community case management strategy to treat childhood infection. Am J Trop Med Hyg 2012; 87:2-5.
- **3.** Sandige H, Ndekha MJ, Briend A, Ashorn P, Manary MJ. Home-based treatment of malnourished Malawian children with locally produced or imported ready-to-use food. J Pediatr Gastroenterol Nutr 2004;39:141-6.
- Kerac M, Bunn J, Seal A, et al. Probiotics and prebiotics for severe acute malnutrition (PRONUT study): a double-blind efficacy randomised controlled trial in Malawi. Lancet 2009;374:136-44.
- 5. Alcoba G, Kerac M, Breysse S, et al. Do children with uncomplicated severe acute malnutrition need antibiotics? A systematic review and meta-analysis. PLoS One 2013;8(1):e53184.

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Long-Term Outcomes in Elderly Survivors of Cardiac Arrest

TO THE EDITOR: In their study of long-term outcomes among survivors of in-hospital cardiac arrest, Chan et al. (March 14 issue)¹ report that 58.5% of patients survived to 1 year and that the 3-year survival rate was similar to that of patients with heart failure. We submit that predicating overall survival estimates on the basis of survival to hospital discharge is misleading. The fact remains that the vast majority of patients who re-

ceive in-hospital cardiopulmonary resuscitation (CPR) die before hospital discharge (Table 1). Since more than half the survivors have moderate-to-severe neurologic disability at discharge, quality-adjusted survival looks even bleaker. For 27% of patients, the use of CPR results in the return of spontaneous circulation but not survival to discharge,³ which lengthens the hospital stay, and possibly suffering, but provides no real