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EDITORIALS

Antibiotics to promote growth in children?

Worth studying in highly selected children, with a close eye on potential harms

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Overt infections are a leading cause of death worldwide in children under 5,¹ and strategies to prevent and treat infections are a cornerstone of child survival programmes. Recent assessments suggest that despite a net increase in the size of birth cohorts, the number of children dying before their fifth birthday has fallen to 6.6 million (uncertainty range 6.3–7.0 million) per year, a 45% reduction from almost 12 million deaths in 1990.² In contrast, the fall in undernutrition has been modest at best. An estimated 165 million children under 5 were stunted in 2011 and an estimated 52 million severely wasted; almost 45% of the current burden from child mortality in under 5s can be attributed to malnutrition.³ Although many risk factors for early child mortality are well recognised, the mechanisms underlying chronic enteropathy and growth failure among children in low and middle income countries remain uncertain.⁴

In a linked paper, Gough and colleagues (doi:10.1136/bmj.g2267) report a systematic review of 10 trials looking for associations between antibiotics, given for a variety of indications, and growth in childhood.⁵ The review included 4316 children (age range 1 month to 12 years) from low and middle income countries. The authors' analysis using random effects models suggests that antibiotic use was associated with increased mean height or linear growth (extra linear growth 0.04 cm/month, 95% confidence interval 0.00 to 0.07) and an extra 23.8 g weight gain per month (95% confidence interval 4.3 to 43.3 g). The authors recommend further evaluation of the growth promoting effect of antibiotics and speculate that the effects may operate through reduction in subclinical infections and beneficial effects on intestinal microbiota.

Several limitations must be considered when interpreting these findings. The 10 included trials were diverse, spanned almost 60 years, and studied a mixed bag of antimicrobial agents and dosages. Some drugs were for prevention, others targeted treatment of specific infections. Treatment periods and follow-up periods varied widely (5 to 575 days and 7 to 658 days, respectively), as did the type of infection under study and the age of the children. The analysis did not take into account the different drivers of growth, especially linear growth, among children aged 1–24 months and those of school age. Finally, the inclusion of trials of metronidazole for giardiasis is questionable,

given the recent findings from a large multicountry study of the causes of diarrhoea suggesting that the organism may not be pathogenic.⁶

Despite these caveats, there is increasing interest in the potential role of antibiotic treatment as an adjunct to other interventions, especially nutrition rehabilitation. In a recent study from Malawi,⁷ stable but severely malnourished children given antibiotics (amoxicillin or cefdinir) for a week in addition to nutritional rehabilitation had significantly better recovery rates and lower mortality than controls given nutritional rehabilitation alone. An important trial of mass treatment with erythromycin (20 mg/kg) in rural Ethiopia also showed a 49% reduction in childhood mortality (cluster adjusted odds ratio for childhood mortality in the intervention communities compared with control communities, 0.51, 95% confidence interval 0.29 to 0.90).⁸ In a trial from Zimbabwe and Uganda, children with HIV who stopped taking daily cotrimoxazole did significantly worse (higher rates of hospital admissions or death) than children who continued taking it. All participants were aged 3 or more and had been taking antiretroviral agents for at least 96 weeks.⁹

Given the evidence of benefits on survival, it is reasonable to anticipate potential benefits of antibiotic treatment on relevant morbidity patterns and possibly growth. The potential relation of subclinical infections with human growth, through possible reduction in immunostimulation and protein diversion to acute phase reactants, has also been recognised.¹⁰ What then are the policy implications of Gough and colleagues' findings? Beyond the obvious need for the rapid diagnosis and treatment of infections in children, the use of antibiotics for promoting growth poses problems. Widespread use of antibiotics—usually in feeds—to promote growth in animals is common and known to promote antimicrobial resistance.¹¹ Although Gough and colleagues suggest that antibiotics might benefit intestinal microbiota, little evidence supports this relation. It is more likely that antibiotics have an adverse effect on intestinal microflora.^{12 13} Any large scale use of antibiotics must be weighed against the possibility of serious long term harm both to individuals and to global populations through the emergence of resistance.¹⁴ There are also obvious cost implications for the commodities and delivery strategies.

There is a clear need for further research in this area to help us understand precisely how antibiotics might promote growth in children. Researchers could start by characterising high risk groups of children who might benefit, such as those with clearly defined subclinical or overt infections, HIV, or severe acute malnutrition. Further trials should be done to confirm the interesting findings from Malawi.⁷ But extending trials of antibiotics to other categories of children, such as those at risk of malnutrition and growth failure, may not be justifiable at this stage. Researchers should instead exploit existing observational cohorts to explore the relation between infections, antibiotic treatment, and nutrition outcomes, including growth patterns, where data are available. The large multicentre Mal-ED studies assessing patterns of growth among infants 0-24 months of age across eight countries (www.fnih.org/work/key-initiatives/mal-ed) are an excellent example of an opportunity to assess the potential impact of antibiotic treatment on linear growth and weight gain using standardised data and definitions. In the interim, continued focus on the 10 recommended evidence based nutrition interventions to promote growth¹⁵ must be prioritised.

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