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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 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.

Mixed bag of trials

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]

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Not yet

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 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 promotes antimicrobial resistance.[11] Although Gough and colleagues suggest that antibiotics might benefit intestinal microbiota, little evidence supports this. 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. 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 example of an opportunity to assess the impact of antibiotic treatment on linear growth and weight using standardised data and definitions. In the interim, continued focus on the 10 recommended evidence based nutrition interventions to promote growth[15] must be prioritised.

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Chronic hypertension during pregnancy

A growing problem that deserves more attention

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Hypertensive disorders of pregnancy are among the leading causes of fetal and maternal morbidity and mortality. Worldwide, 50000 to 60000 women die from pre-eclampsia each year, corresponding to 12% of all maternal deaths.[1 2]

Pre-gestational hypertension has traditionally been considered a benign and stable condition in pregnant women and has attracted little attention from researchers. A linked systematic review and meta-analysis on chronic hypertension during pregnancy by Bramham and colleagues questions this perception and underlines the need for more explicit concern.[3] The review included 55 studies on chronic hypertension during pregnancy, comprising both observational cohort studies and data from interventional trials from 25 different countries.

Hypertension in pregnancy is usually defined as a blood pressure of 140/90 mm Hg or above and proteinuria as a daily protein excretion of 300 mg or above, a protein:creatinine ratio of 0.3 or above, or 1+ on a urine dipstick.[1] However, definitions have changed over time, and hypertensive disorders of pregnancy are now internationally categorised into four clinical categories: gestational hypertension (pregnancy induced hypertension after 20 weeks of gestation), chronic hypertension (pre-gestational hypertension of any cause), pre-eclampsia/eclampsia, and chronic hypertension with superimposed pre-eclampsia.[4] Pre-eclampsia has traditionally been defined as hypertension with proteinuria, but new diagnostic criteria from the American Task Force on Hypertension in Pregnancy include pre-eclampsia in the absence of proteinuria when hypertension is combined with thrombocytopenia, renal insufficiency, impaired liver function, pulmonary oedema, or cerebral or visual symptoms.[1]

Owing to different definitions of hypertension in pregnancy and variations in genetic predisposition, maternal age, and body mass index, the prevalence of chronic hypertension during pregnancy differs between 1% and 5% in different populations. The systematic review and meta-analysis by Bramham and colleagues therefore adds important knowledge on a scale that has not previously been published, and its findings may be extremely useful to healthcare professionals involved in pre-pregnancy counselling and antenatal management of women with chronic hypertension.

The main findings are that pregnancy in women with chronic hypertension is associated with high incidences of superimposed pre-eclampsia (29%), caesarean section (42%), preterm delivery (33%), birth weight below 2500 g (22%), neonatal unit admission (19%), and perinatal death (5%). These incidences are comparable to rates seen in European cohort studies on complications of pregnancy in women with type 1 diabetes.[5]

When outcome data from the US studies were compared with background data from the US national population in 2006, women with chronic hypertension had significantly higher risks of pre-eclampsia, caesarean section, preterm labour, birth weight below 2500 g, neonatal unit admission, and perinatal death. The high prevalence and relative risk of superimposed pre-eclampsia is particular concerning, as the condition is associated with an increased risk of serious complications for both mother and child.

According to the World Health Organization, the epidemic of obesity and subsequent cardiovascular disease, especially in developing countries, is of great concern. In combination with a rising maternal age in many countries, chronic hypertension in pregnancy puts the lives of the pregnant women and their babies at risk and imposes an increasing healthcare burden on society.

What's to be done?

What can we do to prevent the adverse outcomes related to chronic hypertension during pregnancy? Even now, the simple and depressing answer is "not much."

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We know the problem but none of the solutions

Primary prevention initiatives to halt the obesity epidemic have proved to be extremely difficult. Encouraging women to give birth at an earlier age has not been effective either. Smoking cessation in women with chronic hypertension may prevent superimposed pre-eclampsia.[6] Secondary prevention in terms of treatment with antiplatelet agents such as low dose aspirin may reduce the risk of superimposed pre-eclampsia.[7] Antihypertensive treatment in women with chronic hypertension may reduce the risk of progression to severe hypertension but seems to offer no direct benefit for the fetus or improvement in perinatal outcome. Only treatment of blood pressures above 150/100 mm Hg is recommended.[8 9] Even higher cut-off values for treatment have been proposed owing to a known risk of restricted fetal growth as a result of lowered blood pressure.[1] Hopefully, data from the ongoing CHIPS randomised controlled trial will help to identify optimal treatment goals for these women.[10]

The effect of tertiary prevention measures—including pre-conception evaluation of women with pre-gestational hypertension for secondary hypertension and end organ involvement, ultrasound screening programmes for fetal growth, home monitoring of blood pressure, and frequent antenatal visits—could detect superimposed pre-eclampsia and prevent progression to severe complications. However, we still do not know the most effective, safe, and cost effective way to manage it. A more active clinical management regimen with induction of labour in women with gestational hypertension or pre-eclampsia prevents severe hypertension without increasing the rate of caesarean section and is less costly than expectant management.[11] However, the optimal timing of induction in women with uncomplicated chronic hypertension has yet to be determined.

An urgent need remains for research to establish best clinical practice for antenatal care, antihypertensive treatment, and timing of labour in women with uncomplicated chronic hypertension during pregnancy.

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One of the achievements of the US reforms might be to increase capacity to learn faster about the effects of policy

Does US health reform reduce hospital readmission rates?

Not in Massachusetts—insurance expansion alone won't be enough

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In 2012, after the 2010 Affordable Care Act became law but before its full implementation, around 47 million people in the United States were without healthcare insurance. The sweeping provisions of the Affordable Care Act were primarily focused on expanding insurance coverage. An open question is whether such provisions will also affect healthcare utilization and health outcomes.

In a linked paper, Lasser and colleagues studied the effect of reforms in Massachusetts, which passed legislation before the Affordable Care Act and similarly sought to broaden insurance coverage.[1] After reform, the proportion of adults of working age in Massachusetts who were uninsured decreased from 12.5% in 2006 to 5.2% in 2012.[2] Lasser and colleagues examined whether the Massachusetts reforms were associated with favourable changes in readmission rates. Readmissions represent an outcome that imposes a burden on individuals and the healthcare system, which are also amenable to improvements in healthcare quality.

Studying the effect of healthcare insurance strategies on population health and healthcare utilization is challenging. Investigators have so using randomized controlled trials.[3-5] The RAND Health Insurance Experiment of the mid-1970s recruited more than 2000 households and found that higher co-payments within insurance products reduced resource use without large impacts on health or quality of care for most people.[3] For the poorest and sickest patients, however, the reduction in utilization associated with co-payments was harmful on average. Hypertension, for example, was best controlled under free care for these patients.

Another prominent experiment occurred in 2008 when Oregon reopened enrolment to its publicly funded Medicaid programme for families on a low income, which had previously been closed owing to budgetary pressures.[4] Policy makers chose random lottery as the fairest way to allocate the approximately 10000 available places to those on the waiting list. Although unconventional, this

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Where Massachusetts leads

policy resulted in an important opportunity to study the impact of Medicaid.

Not surprisingly, lottery winners reported increased financial security, and catastrophic financial costs were almost eliminated. Compared with the control group, lottery winners also reported that they were more likely to have a usual doctor, and they had more visits to doctors' offices, prescriptions, and recommended preventive care.[4] Medicaid was associated with improvements in self reported health status and depression, though findings for more objective measures of health (such as cholesterol level) were ambiguous or neutral.[6] However, Medicaid patients experienced around 40% more emergency department visits per person than did the controls.[7] These increases were most noticeable for conditions likely treatable in primary care, suggesting weaknesses in the care services received in that setting.

Randomization is useful because it produces comparable treatment groups, but it can be difficult to conduct in a policy setting, and most studies must make use of observational designs. Because the insurance expansion in Massachusetts occurred across the entire state (see web extra on bmj.com), Lasser and colleagues employed a difference in differences design using larger control states in the same region of the country to try to isolate the effect of what happened in Massachusetts.

Risk adjusted, 30 day readmissions are a useful assay for the effect of healthcare reform. Readmission risk is likely related to the quality and safety of patient care during hospital stay, the transitional care services, and access to care and support after hospital discharge.[8 9] It is plausible that, in Massachusetts, the lower cost of care to patients resulting from insurance might mean better access to primary and outpatient care services after hospital discharge, thereby reducing the risk of readmission.

However, the hypothesized benefits failed to emerge. After reform, Massachusetts saw a faster increase in readmission rates than two nearby states—although differences were small (odds ratio 1.02, corresponding to an increase in the readmission rate from around 14.4% to 14.5%).[1] This finding was similar to the Oregon experiment, which found no impact on readmissions.[4] Previous studies in Massachusetts have reported increases in utilization of preventive care after reform,[10] more patients having usual places of care,[10] improvements in self reported health status,[11] and increases in emergency department visits.[12]

No guarantee of access or affordable care

It is hard to generalize from these studies to the effect of the Affordable Care Act, as the context and populations are so different. Ultimately, healthcare reforms are complex interventions, the effect of which depends on the local context. In the United States, the wide range of implementation strategies among the states further complicates this issue. However, the findings from Massachusetts and Oregon, including the lack of reductions in readmissions, suggest that more than insurance coverage is needed to produce major gains in outcomes. Indeed, by itself insurance does not guarantee access to needed services, or even affordable care.[13]

Because insurance is not enough by itself, the Affordable Care Act does have a broader aim to improve both the quality and the efficiency of care. The act has embedded within it the possibility of testing new payment and service delivery strategies.[14] In addition, the act's hospital readmissions reduction program cuts payments to hospitals for readmissions within 30 days of discharge after an initial stay for certain conditions.

It is too early to tell how the wide range of initiatives included in the Affordable Care Act will fare, although readmission rates now seem to be decreasing nationally.[15] One of the achievements of the US reforms might be to increase capacity to learn faster about the effects of policy.

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Promoting and preserving authenticity will be difficult; there is no simple rubric to assess authenticity, nor a specific curriculum to teach it

Medical education's authenticity problem

Why we do what we do, and who we are, are often just as important as what we do

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Medical education is punctuated by gating mechanisms, and anyone involved knows the unsavoury and contrived behaviors that this often breeds. At each stage of their training, aspiring physicians are pressured to shape and reshape their activities, interests, and values to meet the expectations of selection committees, attending physicians, and preceptors.

The notion of authenticity provides a useful framework for examining the impact of these dynamics on the development of new physicians. The term, popularized by Harvard Business School professor Bill George, entails discovering, understanding, and being faithful to your core values and purpose. Instead of emulating the characteristics, traits, or practices of others, authentic individuals interrogate their life experiences to discover their values and purpose through a process of continuous self reflection.[1]

Current dynamics in medical education are often at odds with authenticity. Selection requirements for undergraduate and graduate medical training lead aspiring physicians to appropriate and proclaim interests that are often disingenuous. Junior doctors hoping for selection into competitive training programs are pressured to research and publish, despite the fact that most will not pursue a career in academic medicine. In the United States, prospective medical students feel compelled to work in the laboratory or volunteer at a local hospital, whether or not they have a genuine desire to do so.

Trial and error is an inherent component of career exploration, and students will inevitably find and lose interests along the way. However, physicians in training now spend the formative years of their personal and professional development—nearly two decades—emulating others and conforming to expectations, often at the expense of discovering their true values, motivations, and purpose.

The challenge of authenticity extends beyond selection processes, permeating the curriculums within which medical students and junior doctors train. Movements towards standardized learning and assessment often leave little room for reflection, introspection, and self discovery. This is particularly glaring in attempts to standardize communication skills—the heart of the patient encounter. At various points in our training, we were taught specific language, behaviors, actions, and reactions to use when interacting with patients.

Stiff, scripted, or fake

This focus on product, not process, can result in physicians being perceived as stiff, scripted, or even fake. As an example, earlier this year one of us (BWP) witnessed a first year medical student who, when hearing that a patient recently lost a leg, asked: "was the amputation hard for you?" The woman quipped back "well, they cut my leg off." Normally charming and affable, the student's natural communication style was stymied by trying to conform to the standards outlined in his education. Instead of focusing on emulating best practices, curricular efforts should help students develop an authentic, genuine style of practice consistent with their personality and character. Empathy and humanism flow from authenticity.

Rate students by depth of interests and achievements

It is worth noting that efforts to counteract these trends have increased. In the US, the Association of American Medical Colleges' holistic review project is working to promote a more comprehensive and individualized assessment of medical school applicants and their character.[2] Increased commitment to rating students by the depth of their interests and achievements, rather than by their engagement with specific activities, will help build a culture of self discovery and authenticity among prospective medical students. It should draw passionate people with diverse interests into the profession. Furthermore, medical education bodies across health systems continue to refine their expectations for undergraduate training, increasing the focus on the humanistic dimensions of medicine and the importance of self reflection.[3 4]

But medical schools and training programs implementing these reforms face a paradox: reorienting around authenticity requires standardizing experiences and defining authenticity. With formalized requirements and expectations in place, gamesmanship and emulation will remain. Despite this inevitable tension, we believe that authenticity must assume a more prominent position among our educational priorities. According to Fish and de Cossart, teaching and assessment need to focus "not only the professional's visible behaviour, but also the motivations that drive . . . the practitioner's underlying humanity and self-knowledge."[5]

Promoting and preserving authenticity will be difficult; there is no simple rubric to assess authenticity, nor a specific curriculum to teach it. But this should not detract from its importance as a core value in both medical education and medical practice. Evidence suggests that a workforce of authentic physicians can yield improvements across the spectrum of care. Self awareness and reflection—hallmarks of authenticity—are strongly correlated with resilience to burnout among physicians.[6] An authentic workforce can also improve the performance of clinical teams.[7] Finally, authentic people excel at building strong genuine relationships that motivate, inspire, and empower those around them[8]—traits that can help physicians form strong therapeutic relationships with their patients.

To capture this potential, it is crucial to understand the importance of authenticity, and the current structural, policy, payment, and managerial dynamics that go against it. As global efforts at reform progress, we hope to see authenticity assume a place alongside patient centered care, practice based learning, and system based practice as essential priorities for medical education and medical practice.

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