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**EDITORIALS**

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**Improving child survival through vitamin A supplementation**

Fine tuning the dose and delivery mechanism could further improve outcomes

Worldwide, nearly 8.8 million children die each year before they reach their 5th birthday.

More than two thirds die from infectious diseases such as pneumonia, diarrhoea, and malaria. Although these are sobering figures, childhood mortality has been substantially reduced over the past decade partly as a result of the expansion of child survival interventions to prevent and treat major causes of childhood mortality.

In the linked systematic review and meta-analysis, Mayo-Wilson and colleagues assess the effects of vitamin A supplementation on mortality and morbidity in children 6 months to 5 years of age. Routine preventive treatment of all children 6-59 months of age with high dose vitamin A supplements is a core intervention to improve child survival supported by Unicef, the World Health Organization, governments, and donors in areas of high mortality and endemic vitamin A deficiency. Capsules are now distributed biannually in at least 60 countries, with average annual coverage rates nearing 80%.

Initially launched as an initiative to prevent xerophthalmic blindness, universal vitamin A supplementation was expanded as a life-saving intervention mainly on the basis of meta-analyses that showed average reductions in all cause mortality of 23-30% coupled with low costs of implementation.

Since its discovery in 1913, no nutrient has been as well studied or as fraught with controversy as vitamin A. Critics of high dose vitamin A supplementation have expressed concerns about the inconsistent evidence base for such programmes, arguing that not all trials of vitamin A supplementation have shown protective effects on all cause mortality and that it may increase the incidence of respiratory infections, particularly in children who are not vitamin A deficient.

Proponents argue that most studies have found beneficial effects on all cause mortality, and that evidence on other major causes of death including diarrhoea and measles has been fairly consistent.

Lingering uncertainties were compounded by the presentation at the 2007 Micronutrient Forum of findings from the largest randomised trial ever undertaken, the DEVTA (de-worming and vitamin A) trial.

This cluster randomised open control trial of biannual supplementation with 200 000 IU vitamin A investigated more than one million children aged 12-59 months in rural north India. Preliminary results of all cause mortality were null, but the investigators noted that the results were also consistent with a reduction of 12% (relative risk 0.96, 95% confidence interval 0.88 to 1.05). Four years later, the study remains unpublished for uncertain reasons. Until this trial is published and its quality assessed it cannot be properly evaluated or integrated into the larger body of evidence. Yet the null findings, particularly given the large size of the trial, have left lingering questions.

Is vitamin A supplementation effective? Might harmful effects of supplementation on some infections be cancelling out beneficial effects on others? Do changes need to be made to the delivery strategy, such as reducing the dosage and increasing the frequency or using a targeted rather than universal approach?

Mayo-Wilson and colleagues’ meta-analysis tackles at least some of these questions. It reports a 24% reduction in all cause mortality associated with synthetic oral vitamin A supplements, a finding that is virtually unchanged from previous analyses, despite the inclusion of nine extra studies.

The meta-analysis is unprecedented in its depth and methodological rigour, incorporating a wider number of morbidity and mortality outcomes than previous reviews of preschool vitamin A supplementation. This is important because some previous reviews have examined either morbidity or mortality, but not both, leaving questions as to whether inconsistent findings may have resulted from differences in approaches to inclusion and exclusion criteria versus other sources of heterogeneity.

The results of the sensitivity analysis including the DEVTA trial also help to allay some of this uncertainty. Its inclusion reduces the all cause mortality benefit from 24% to 12%, yet the result remains statistically significant and clinically meaningful. Vitamin A supplementation has been ranked as one of the most cost effective child survival interventions. Even if it only saves half as many lives as previously estimated, it is probably still exceptionally cost effective and worth funding.

Although the review is an important step in helping to clarify the effects of vitamin A on mortality and morbidity, several important questions remain. Given that 41% of all deaths in children under 5 take place during the first 28 days of life, could vitamin A supplementation of this younger age group help to accelerate progress? Trials in Ghana, India, and Tanzania coordinated by WHO and funded by the Bill and Melinda Gates Foundation should help to assess the potential for vitamin A to save newborn lives.

Another question that needs further research is the role of vitamin A supplementation in malaria. Just one study has examined the effect of vitamin A supplements on the incidence of malaria, and it showed a significant 30% reduction (0.70, 0.57 to 0.87). Given that malaria is responsible for 8% of deaths in children, further research on this association is warranted.

Most national vitamin A programmes supplement children twice a year, yet evidence suggests that more frequent...
supplementation could reduce mortality even further.\(^5\)
Research into alternative dosing approaches and delivery mechanisms, with proper evaluation, might enable programmes to be more effective. Lastly, as previous meta-analyses have stated, no more placebo controlled trials of preschool vitamin A supplementation are needed. Instead, effort should focus on finding ways to sustain this important child survival initiative and fine tune it to maximise the number of lives saved.

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**Adenoidectomy in children with recurrent upper respiratory infections**

Immediate surgery seems to offer no benefit over initial watchful waiting

Although recurrent upper respiratory tract infections in childhood are self limiting, with high rates of spontaneous recovery,\(^7\) they are associated with high healthcare costs and frequent visits to the doctor. Most of these infections are caused by viruses. Generally, they are associated with little morbidity but predispose children to complications such as otitis media, tonsillitis, and sinusitis, which cause further morbidity.\(^8\) About a fifth of preschool children have recurrent upper respiratory tract infections, and many of these are referred to ear, nose, and throat surgeons for upper airway surgery, including adenoidectomy.\(^7\)\(^,\)\(^8\)

Adenoidectomy restores normal breathing through the nose if the hypertrophied adenoid obstructs the nasopharynx. It can also improve hearing in children with otitis media, sinusitis, or sleep apnoea. A systematic review in 2010 of adenoidectomy in children identified only two randomised controlled trials that included upper respiratory tract infections as an outcome.\(^9\) One was methodologically weak and the other included only children who primarily had otitis media.\(^7\)

The generalisability of the results warrants consideration. Ear, nose, and throat surgeons in the respective hospitals diagnosed and selected eligible children. Because there are no internationally accepted guidelines for the diagnosis and treatment of recurrent upper respiratory tract infections, diagnosis is likely to vary between doctors. Furthermore, rates of adenoidectomy vary considerably nationally and internationally,\(^7\)\(^9\) and rates for recurrent upper respiratory infections alone have been estimated to be 12% in the United States and 60% in the Netherlands (http://statline.cbs.nl/statweb) over the past decade.\(^10\)

Rates of upper respiratory tract surgery vary nationally and internationally. Clinicians seem to be similar in their uncertainty regarding indications for procedures, and variations in surgery rates among countries appear to be more characteristic for the procedure than for the country in which it is performed.\(^8\) To date, no consensus exists to help surgeons decide which children with upper respiratory tract infections will benefit from adenoidectomy. Accordingly, this lack of exact criteria for surgery may have affected the selection of children to surgery in the current study and also the primary and secondary out-

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Sex differences in the risk of cardiovascular disease

The accelerated risk at menopause may not be as clear as previously thought

Long before the landmark Women’s Health Initiative clinical trial studied the effects of hormone replacement therapy (HRT) on cardiovascular disease in postmenopausal women, several questions framed the debate about whether menopause truly represented a period of equalisation between women and men in the risk of cardiovascular disease.1,2 Was menopause a pathophysiological turning point for women, or was the acceleration in risk due to natural ageing processes, independent of the hormonal effects of menopause? Recent studies have asked whether cardiovascular disease risk factors lead to menopause rather than the other way around.3 Still, the overarching question remains: if a sex gap exists in the risk of cardiovascular disease, how can we use our understanding of what drives this difference to take better care of our patients and ultimately to close the divide?

The linked study by Vaidya and colleagues substantially extends our understanding of the epidemiology of sex differences in death from ischaemic heart disease.4 The authors used longitudinal data in men and women from the United States and from England and Wales to quantitatively test whether ischaemic heart disease mortality significantly changes (either accelerates or decelerates) around the estimated time of menopause (45-54 years of age). They found that, unlike deaths from breast cancer, rates of death from ischaemic heart disease did not rise around the estimated time of menopause in women. Interestingly, a deceleration in the rate of death from ischaemic heart disease was seen in men at age 45, which the authors argue might account for the perceived equalisation of risk in women at the time of menopause. The use of longitudinal data, two large geographically separate cohorts, and statistical methods to test for the ischaemic heart disease mortality rate changes strengthen the authors’ observations.

While Vaidya and colleagues’ results seem to exonerate menopause as the sole driver of sex differences in death from ischaemic heart disease, the story may not be that simple. Current data from clinical trials do not support a protective effect of maintaining a pre-menopausal hormonal milieu; in fact, HRT in postmenopausal women was associated with modest increases in cardiovascular disease compared with placebo.5 However, debate continues about whether HRT is efficacious in younger, recently postmenopausal women compared with older, remotely menopausal women.6 With the so-called “timing hypothesis” as yet unresolved, evidence-based practice guidelines appropriately advise that HRT should not be used primarily for the prevention of cardiovascular disease in postmenopausal women.

Vaidya and colleagues’ study confirms previous reports of a deceleration in the rate of ischaemic heart disease among men at age 45 years. The concept of a male clomacteric or “andropause” has been popularised in the lay press and has been referred to in the scientific literature as late onset hypogonadism or male testosterone deficiency. Testosterone levels fall steadily in men between their 30s and 90s.7 However, testosterone deficiency has not been

convincingly linked to incident cardiovascular disease in men and experts have called for more scientifically rigorous clinical trials of androgen replacement. Biological processes aside from those related to sex hormones might account for the increased ischaemic heart disease risk among younger men, and this would be an interesting area for further study.

Vaidya and colleagues show that ischaemic heart disease in women is a life course disease that steadily marches forward, showing no midlife acceleration. However, this does not mean that cardiovascular disease risk factors in women are entirely “sex neutral.” Increasing evidence shows that factors related to pregnancy—such as a history of pre-eclampsia, gestational diabetes, preterm delivery, and having babies with low birth weight—increase the risks of long term cardiovascular disease in women. Indeed, for the first time, guidelines on preventing cardiovascular disease in women from the American Heart Association advocate that doctors take a reproductive history when stratifying the risk of cardiovascular disease. Knowledge of pregnancy related risk factors may help physicians identify women who are at risk earlier than midlife. Whether these factors confer an independent risk of cardiovascular disease above and beyond classic risk factors in women is still uncertain, but is an important area for further study.

Although use of epidemiological data to answer clinical questions is not without its faults, a major strength is that it generally offers a bird’s eye view rather than a keyhole vantage point. To answer the challenging question of what drives differences in cardiovascular disease in men and women over their lifespan, a combination of science from both far and near perspectives will be needed.


 Provision of health information for all
A major organisation should support global efforts

High quality information is essential for good health, yet many individuals, practitioners, and health organisations—particularly in low and middle income countries—lack access to information. This problem has been highlighted many times, and Health Information for All 2015 (HIFA2015) was founded in 2006 with the aim that “by 2015 every person worldwide will have access to an informed healthcare provider—lack of relevant, reliable healthcare information will no longer be a major contributor to avoidable death and suffering” (www.hifa2015.org). It is unlikely that this ambitious goal will be achieved.

In HIFA2015’s definition, the term “healthcare providers” includes mothers and family caregivers, in recognition that their basic knowledge and decisions are crucial to survival. In many countries in Africa more than 80% of children die before they even reach a health facility. The term “healthcare information” refers to health knowledge for prevention and treatment of disease rather than routine statistical data. HIFA2015 now has 5000 members from 200 organisations in 158 countries, and it has four global forums—HIFA2015, CHILD2015, HIFA-Portuguese, and HIFA-EVIPNet. Most of those who contribute to the forums come from low and middle income countries. The organisation has a three pronged strategy of communication (bringing together a critical mass of agents for change), understanding (of information needs and how to meet them), and advocacy (persuading governments, funding agencies, and others to invest in cost effective health information services). There has been progress in access to electronic journals, thanks to initiatives such as the HINARI Access to Research in Health programme and the open access movement, but little progress in meeting the information needs of frontline healthcare providers and ordinary citizens in low resource settings.

The work of HIFA2015 has been achieved with an income of less than £30 000 (£33 300; $48 000) a year, a £10 000 of which comes from the BMA. More than 100 health and development organisations worldwide have committed in principle to the HIFA2015 goal, but no major funding agency has done so. Some $160bn is spent annually on health research, and it seems odd that no organisation will fund improving access to that information. The Rockefeller Foundation is funding an evaluation of HIFA2015 that ironically costs more than the programme being evaluated.

One of the reasons for the lack of commitment may be the lack of clarity of the scale of the problem. The World Health Report 2010 estimated that more than a billion people lack access to healthcare. There is virtually no access to high quality information in many rural areas of low income countries. The consequences are highlighted in the HIFA2015 report: eight in 10 caregivers in developing countries do not know

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New NICE guidelines for hypertension

Ambulatory monitoring is to become key

The recent updated guidance from the National Institute for Health and Clinical Excellence (NICE) on the management of hypertension in adults will have far reaching implications for day to day practice in the United Kingdom.1 2 The guidelines were developed in partnership with the British Hypertension Society and have 65 recommendations, 36 of which are new, with 12 listed as key priorities. Although these figures may seem daunting, closer scrutiny shows that most of the changes have evolved from previous guidelines and should be relatively straightforward to incorporate into clinical practice.

For the first time targets have been partially relaxed. Admittedly this applies only to people aged 80 or more, in whom a target blood pressure lower than 150/90 mm Hg is recommended. The previous target of 140/90 mm Hg is retained for everyone else, and this will continue to be a challenge in primary care.3 However, the guidelines clearly state that individual needs and preferences must be taken into account.4 They acknowledge that a balance must be struck between achieving targets and the realities of adherence to treatment and possible distressing side effects—particularly symptoms of postural hypotension.

The most noticeable change with regard to drug treatment concerns thiazides, which are no longer recommended as first line drugs unless other indications exist. Calcium channel blockers are preferred first drugs for hypertension,3 4 5 6 7 8 9 10 Calcium channel blockers are preferred first drugs for hypertension,3 4 5 6 7 8 9 10

The two key symptoms of childhood pneumonia, four in 10 mothers in India believe that they should withhold fluids if their baby develops diarrhoea, and three in four doctors caring for sick children in district hospitals in seven low income countries have poor knowledge of the leading causes of death in children.8 But these are just anecdotes. A large scale study is needed of the information needs of health providers in low income settings and how well those needs are being met. This could provide the stimulus for global action.

Another reason may be that improving information supply requires more than simply shifting textbooks to Africa or providing internet access. There is a need to create a culture of valuing, generating, and using information—what has been called the knowledge cycle.4

Not only is the problem complex it is also not sexy. Funders are much keener to put money into drugs, vaccines, and bed nets than they are into something as nebulous as information access. Yet information and the capacity to act on that information is the first building block of an effective health system, as outlined in WHO’s framework for action on health systems strengthening.1

Major funders may hope that technology or the private sector will solve the problem. However, internet access is slow and expensive in poorer countries, and it is available to only 11% of people in Africa, 0.5% in Ethiopia, and 0.9% in Bangladesh.9 Mobile phones are becoming more available in low income countries, but much more is needed to improve access to information. And although the private sector is the main supplier of information in the rich world, public-private partnerships may well be needed to improve information access in poorer countries, in the same way that the Global Alliance for Vaccines and Immunisation was needed to improve access to vaccines.

Fiona Godlee and others called in the Lancet in 2004 for WHO “to take the lead in championing the goal of ‘Universal access to essential healthcare information by 2015’” and for “an international collaborative group along the lines of the Global Fund.”7 Since then WHO has provided moral and technical support for HIFA2015, but it has not led a major initiative and there is no global fund. One of the strengths of HIFA2015 is that it is an international collaborative group that includes the full range of stakeholders, from senior WHO executives in Geneva to rural health workers in Bangladesh, with a predominance of people from low and middle income countries. What it lacks are funds. Rather than start another organisation the best way forward would be for a major funder to recognise that improved health information is fundamental to global health improvement and development and offer substantial support, not just funds, to HIFA2015.

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Ambulatory monitoring should now be offered to everyone with a blood pressure of 140/90 mm Hg or more in the clinic

need not be changed. There are few surprises in the other recommendations for drug treatment, including optimal combination treatment.

If all this seems incremental, the guidance on diagnosing hypertension is more radical. The guideline recognises the overtreatment of people with “white coat” hypertension and now recommends that ambulatory monitoring is offered to all patients with blood pressure values of 140/90 mm Hg or more in the clinic, although for severe hypertension (≥180/110 mm Hg), immediate treatment should be considered. Target organ damage should be investigated and cardiovascular risk formally assessed as part of the diagnostic investigation. A recent systematic review found that neither clinic nor home measurements have sufficient sensitivity or specificity as a single diagnostic test compared with ambulatory monitoring, which would result in more appropriately targeted treatment.

This recommendation has important investment implications, especially for primary care, in terms of funding and maintenance of new equipment, staff training, and deployment costs. However, the cost effectiveness analysis that accompanies the new NICE guidelines supports the case for ambulatory monitoring by concluding that the additional costs incurred are counterbalanced by cost savings. It found that ambulatory monitoring was cost effective for men and women of all ages and cost saving for all groups (40-75 years). The median cost of a single ambulatory monitoring device was estimated at £1016 (£1160; £1638), and £380 was needed each year for device servicing, calibration, and replacement of parts. Although consultation costs are shown, it is unclear whether these figures also include the computer support, staff training, and administration time that will be needed. Upfront primary care costs could therefore be higher and will vary appreciably between large and small general practices.

Is the case for comprehensive switching to ambulatory monitoring convincing enough? The evidence is persuasive: the benefits are that drug treatment will be targeted at those most likely to benefit because ambulatory monitoring is better than blood pressure measurement in the clinic at predicting those who will have cardiovascular events in the future. It should reduce inappropriate drug treatment in the estimated quarter of patients whose clinic blood pressure is inflated by the white coat effect. But ambulatory monitoring may not be the only option. In a recent meta-analysis, neither of the two studies of home blood pressure monitoring were inferior to ambulatory monitoring for predicting cardiovascular events (both were better than clinic blood pressure). Home blood pressure monitoring may be simpler to implement, and the NICE guidance recognises it as a suitable alternative for people who cannot tolerate ambulatory monitoring and for assessing response to treatment in people with white coat effect, as an adjunct to clinic blood pressure monitoring. It could also be considered as an interim option for general practices that presently lack ambulatory monitoring equipment.

Several important questions about ambulatory monitoring remain, including uncertainties about summary readings and the frequency of assessment. Although the role of ambulatory monitoring in the accurate diagnosis of hypertension has been further clarified, its optimal role still needs to be established for monitoring response to antihypertensive treatment.

Considerable challenges in implementation remain. On the basis of traditional clinic measurements, at least a quarter of all adults in the UK have hypertension—more than half of those over 60 years—and 12% of general practice consultations in 2006 were for hypertension. Prevalence will increase with an ageing population. General practices and emerging consortia should therefore work closely with secondary care to develop local ambulatory monitoring implementation plans, which respond robustly to this step change in the diagnosis of hypertension.

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