Intestinal nematode infection and anaemia in developing countries

Deworming and iron supplementation are cheap and effective

CDC

RESEARCH, p 1095

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In low and middle income countries, about 1.2 billion people are infected with roundworm (*Ascaris lumbricoides*), and more than 700 million are infected with hookworm (*Necator americanus* or *Ancylostoma duodenale*) or whipworm (*Trichuris trichiura*).[1] Infection with intestinal nematodes is linked with poverty because of its association with unsafe disposal of faeces, in which the infective stages develop.

Infection can occur in all age groups but is most common in school age children. Though infection can be fatal,[2] the major burden of disease is due to its insidious effects on physical and cognitive development during childhood.[3] Anaemia, for example, is commonly associated with infection and can impair cognitive ability.[4] In areas of high prevalence of infection in East Africa, 15-25% of anaemia in schoolchildren is due to hookworm infection.[5]

In this week's *BMJ*, a systematic review of randomised trials by Gulani and colleagues assesses the effect of routine deworming on haemoglobin concentrations.[6] It finds that deworming increases haemoglobin by 1.71 g/l (95% confidence interval 0.70 to 2.73), which could translate into a small (5-10%) reduction in the prevalence of anaemia. However, some elements of the study design suggest that this may be an underestimate of the impact, and that the results may have broader implications for practice.

Most deworming programmes assume that it is unnecessary to diagnose the specific infection as the commonly used benzimiadazoles are effective against common worm species. This can make it difficult to assess the results of clinical trials because the species of worm profoundly influences the risk of anaemia.

Hookworms adhere to the gut mucosa, feed on blood, and leave areas of intraluminal microhaemorrhage when they detach. Daily blood loss due to *A duodenale* is estimated at 0.2 ml per worm, equivalent to 100 ml in heavy infections. This is about 10 times greater than with *N americanus* infection, and surveys in Africa confirm that anaemia is more common with *A duodenale* infection.[7] Blood loss during whipworm infection comes mainly from the inflamed gut mucosa, and at 8.6 ml/day is less than with hookworm. Blood loss is not typical of roundworm infection, and it is unclear whether the low serum retinol and serum ferritin concentrations associated with fat malabsorption result in anaemia.[8] Therefore, the review by Gulani and colleagues does not, or perhaps could not, differentiate between the effects of different worm species in contributing to anaemia and the potential impact of deworming.[6]

Not differentiating between species and anthelmintics also makes it difficult to assess the effects of specific drugs. The World Health Organization recommends the use of albendazole, mebendazole, pyrantel, and levamisole. Of the 14 studies included in the review, one used an anthelmintic that is no longer recommended (bephenium hydroxyl naphthoate), three used mebendazole, and 10 used albendazole. While both benzimidazoles have similar high efficacy against roundworm and moderate efficacy against whipworm, single dose mebendazole is much less effective against hookworm, with cure rates typically below 60%.[9] In almost a third of the trials, treatment (dose and choice of drug) was less than optimal for the hookworm infection that would probably contribute most to anaemia. Thus, the review probably underestimated the effect of deworming on anaemia.

So what practical lessons does the review offer? Firstly, the number of doses of anthelmintic did not predict effectiveness. This suggests that less frequent and therefore cheaper approaches may be adequate; this should encourage a review of current guidelines on the frequency of anthelmintic treatment in the community. Secondly, analysis of the studies (around half) that gave iron supplements and anthelmintics found that coadminstration of iron significantly increased the size of the effect of deworming on anaemia.

Available evidence suggests that removing the source of blood loss alone is unlikely to replenish iron stores in the short term,[10] and the review provides more evidence of the value of combining deworming with iron supplements.[11] The lack of iron supplementation in half the studies would also tend to underestimate the effectiveness of the approach in improving haemoglobin concentrations.

Because the review tended to underestimate the impact of deworming, and given the remarkably low cost of deworming and iron supplementation,[12] combining the two approaches in programmes for young people should be encouraged. Given the high prevalence of both anaemia and worm infection in pregnancy,[13] a similar review is needed in pregnant women.

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The role of pharmacists in primary care

Needs reconsideration in light of the evidence of an unfavourable impact on patient outcomes

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The National Health Service recently launched *Choosing health through pharmacy*,[1] an initiative aimed at enhancing the contribution of pharmacists to improving the public's health and reducing health inequalities. The initiative assumes that, on the basis of their knowledge, skills, and proximity to the public, pharmacists are an untapped resource for health in the United Kingdom. However, evidence that pharmacists' involvement with the public improves health outcomes is mixed.[2 3]

This week's *BMJ* includes two studies about the role of community pharmacists in primary health care.[4 5] In the first, Salter and colleagues explore the role of pharmacists in giving advice to older patients during medication review.[4] They find that although many opportunities were available for pharmacists to offer advice, information, and instructions to patients, this was often resisted or rejected. This caused "interactional difficulties" during consultations between pharmacists and patients. In the second study, Holland and colleagues report a randomised controlled trial assessing whether medication review and advice by community pharmacists reduced hospital admissions or mortality in patients with heart failure, compared with usual care.[5] It found no significant difference in hospital readmissions at six months (134 *v* 112 in controls; rate ratio 1.15, 95% confidence interval 0.89 to 1.48), quality of life, or mortality. The fact that both studies using different research methods produced unfavourable findings raises important questions about the role of pharmacists in primary health care.

Holland and colleagues' findings may have been negative because their trial assessed the global impact of the intervention rather than outcomes related to specific aspects of the interaction between the pharmacist and the patient. This would mean that the relative, and potentially positive, contribution of these different aspects could not be ascertained.

Salter and colleagues are clearer about the negative impact of pharmacists giving advice, and emphasise the potential harm of (unsolicited) advice on patients' sense of competence and self governance. By analysing the discourse between pharmacists and patients they highlight the problems with medication review where advice giving is didactic and controlled by professionals. Their conclusions support the growing body of literature in which the relationship between the "expert" and the lay person is deconstructed,[6-8] and where "concordance" around the goals of treatment is prioritised.[9] This literature suggests that healthcare professionals have the greatest impact when they give serious consideration to patients' agendas for health and how they rationalise decisions.

Although the overall findings of the studies are negative, there are positive aspects that the authors do not consider. Salter and colleagues do not elaborate on their assertion that pharmacists found many opportunities to offer advice, information, and instruction (presumably because of problems with elderly patients' drug regimens). Holland and colleagues look at this aspect in more detail. They report that pharmacists' home visits to patients with heart failure resulted in 384 recommendations to general practitioners. These recommendations were made despite patients having unusually high levels of adherence to their drug regimens. In other words, the recommendations to doctors were not related to non-adherence.

The recommendations reported by Holland and colleagues resulted in visits to doctors, drug reviews, and sometimes (re)admission to hospital. Holland and colleagues interpret the outcome of increasing hospital admissions as negative (assuming that intervention by a pharmacist should reduce admissions). However, any responses to pharmacists' advice, including readmission to hospital, may have reduced iatrogenic illness and possibly saved lives. The study did not assess these specific actions.

Pharmacy as a profession has reoriented its practice from a clinical service model to a pharmaceutical care

model[10]—a practice philosophy with parallels to the concept and goals of the patient centred care model adopted by medicine.[11] Both models proclaim a commitment and responsibility to enhance outcomes for patients through developing an alliance between the professional and the patient. Pharmaceutical care is uniquely focused on the pharmacists' responsibility for the patient's drug related needs. Those needs are not limited to specific clinical problems and goals but to all of the patient's medications, medical conditions, and outcome parameters.[10]

Yet public recognition of the potential role of pharmacists in reducing the medical and economic costs of inappropriate drug use is lacking. This might be because any positive impact that pharmacists may have is not captured by the appropriate study designs. It might also be due to patients' perceptions of the status of the pharmacist in the health professional hierarchy. This is shown by Salter and colleagues with reference to many examples where patients "call on the higher authority of the doctor" as a means to challenge the advice given by the pharmacist.

If the Department of Health is to provide pharmacists with a more expansive role in public health in the UK, a campaign is needed to educate the public and the medical community about the harms of inappropriate use of medication and how pharmacists can be a potential resource for patients who take medicines. A strategy to increase the public's exposure to pharmacists working in primary care, separate from the dispensing of products—the new pharmaceutical carepractitioner model[10]—may help. Finally, the agenda for research into the impact of pharmacists on health should be refined. A good start would be to explore the nature of the drug related problems in elderly people highlighted by Salter and colleagues,[4] and what specific recommendations were made to the doctors of patients with heart disease in Holland and colleagues' study.[5]

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The future of specialist training in the UK

Doctors' anger and mobilisation are at last forcing a rethink

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The United Kingdom's doctors are for once united, but not for the moment under the auspices of the BMA, their trade union and professional body. Instead, their growing outrage about new rules for junior doctors' specialist training has found its voice through two pressure groups, while the chairman of the BMA's council has been forced to resign for failing to reflect members' views. RemedyUK's legal challenge (see p1075)—due to conclude after the *BMJ* goes to press—is likely (even if they lose their case) to force a rethink of the way in which training posts are filled, while surveys of doctors run by an ad hoc group of senior academics under the leadership of Morris Brown (see bmj.com/cgi/eletters/334/7601/0#165660) have brought consultants and junior doctors together in a rare show of solidarity. Jim Johnson's unprecedented resignation (see p 1074), only weeks before the organisation's annual meeting at which he planned to stand down, bears further witness to the depth of feeling across the profession and within the BMA. Anger about the Medical Training Application System (MTAS) may have been the touch paper that set off this immediate crisis, but it has its roots in the new specialty training scheme Modernising Medical Careers. The scheme is based on sound and broadly agreed principles—longer contracts offering greater security, competency based training, and more senior supervision—but the manner of its implementation was condemned by the BMA and the colleges, and it led to the resignation last month of its director Alan Crockard. Radically shorter, narrower, less flexible, and less personalised training was aggravated by a rushed and centralised implementation, a rigid and ultimately unfit application system, and a considerable shortfall in the number of training posts. Ignoring advice from the various professional bodies, the Modernising Medical Careers team went for a big bang implementation, not only for new entrants to specialist training but for those already in training posts. The system was not piloted, its ability to discriminate between good and less good candidates was not validated, and (as revealed in RemedyUK's judicial review) the software was neither finished nor tested before it was put in place.

Among the hundreds of postings to medical and newspaper websites in the past few weeks are many proposals for rescue from the immediate crisis, some of

them more feasible than others. RemedyUK's position, initially calling for the whole system to be scrapped, is now to honour job offers but only as temporary appointments that will not count towards specialist training. Morris Brown's position is that the temporary appointments should be retrospectively accredited towards training. While both groups have touched a nerve and given the BMA a master class in how to mobilise members, neither are representative bodies that can be held to account. The BMA is. Last month's junior doctors' conference did not support temporary posts, taking the view that most candidates are likely to be accommodated through further iterations of the first round of interviews and extended provision of interviews and posts in round two.

No one doubts that this is an enormous mess. We will know more about where to apportion blame when John Took's independent review reports at the end of the year. Meanwhile, the profession as a whole has suffered a hard knock from which its leaders are clearly keen to learn. Most people I have spoken to acknowledge that the BMA has let junior doctors down. They also feel that the organisation needs to modernise, that it needs to find better ways to stay in touch with its members, and that it needs to find a better balance between representation and leadership and between working with government while remaining strongly independent of it. Failure could put at risk the BMA's official monopoly on representing the UK's doctors. The threat of mass resignations by junior doctors confirms that this is a position the BMA needs continuously to earn.

Now is the time for the profession to put aside it's differences. We need a comprehensive rethink, a chance perhaps to put this miserable episode to good use. We need solutions for the immediate problem, including a better understanding of how many additional posts are needed and how these can be filled with the best candidates. All parties then need to work together—the BMA, the colleges, government, and RemedyUK—to design and pilot a specialist training scheme fit for the future of health care in the UK.

Rationing in the NHS

The BMA asks the right questions but answering them will be difficult

REVIEWS, p 1114

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Over the past two decades or so rationing has been debated more than almost any other area of health policy. However, the debate has been punctuated by periods of relative silence when policy makers have been reluctant to tackle the key problems. The past few years have been one such period as new money appeared to have flushed away old concerns. Now, however, those concerns are back, underlined by the hectic race to balance the National Health Service's books and the realisation that the days of rapid growth in its budget are almost over.

A new factor is adding to these concerns. If in the past the NHS was a model of economy, it was partly because no one had an incentive to maximise activity. But as the new model NHS emerges, payment by results to hospital providers will provide such an incentive. As the NHS inevitably becomes a demand generating machine, so the challenge of accommodating competing demands within a constrained budget will become more acute.

The BMA has therefore rightly made rationing one of the themes of its report on the future of the NHS, published on 8 May 2007.[1] The main point of the report is the need to separate national politics from the everyday running of the NHS. The report recognises that "priority setting and, hence, rationing is inevitable," as it is in all healthcare systems. But if hard choices are inevitable, how are they to be made? The BMA's report suggests a double headed strategy. Parliament "informed by expert professional and public opinion" would determine the "core services" that should be available nationally, and set priorities for the whole NHS. Local health economies, however, would then decide what additional services should be provided from within their budgets.

It appears to be a neat formula. But is it realistic? The report recognises that decisions about who should get what involve social and political choices, as well as professional expertise. However, it also proposes machinery for protecting the NHS from day to day politics, with an independent board accountable to parliament and a much diminished role for the Department of Health. It is not likely that we can have it both ways. If decisions about resources are inevitably political, can the NHS really be protected? Putting parliament centre stage would complicate rather than solve the dilemma. It presumes a constitutional revolution. The House of Commons is a decision reviewing body, not a decision making one. Giving it responsibility for defining core services would imply a new relation between executive and legislature.

But assuming that there are no major institutional changes, and that the Department of Health retains at least a strategic role, the notion of core services—that is, identifying both entitlements and exclusions—remains highly contestable. Many countries have tried to define the menu of entitlements, but in practice excluded services have tended to creep in by the back door.[2 3] More troubling still, the concept of a core service is flexible as it does not necessarily imply a particular level or depth of service; for example, staffing ratios, drug budgets, or the number of diagnostic tests. No doubt some of these can be specified in national service frameworks, but only at the risk of reducing scope for the local professionally led initiatives that the BMA proposals are designed to encourage.

So we come to the second leg of the BMA's strategy—giving more freedom to local health economies. This is a

welcome recognition of the central role of primary care trusts. Many trusts have set up the machinery for prioritising competing claims on resources, deciding what drugs are to be prescribed, and scrutinising referrals.[4 5] Their methods for doing so vary, as do the decisions taken. Furthermore, we know that there are large unexplained variations in what different primary care trusts spend on particular services, such as cancer and mental health.[6] So we come to some crucial questions. When does local discretion become postcode rationing? If central prescription is at odds with local priorities—as in the case of some National Institute for Health and Clinical Excellence recommendations[7]—which should prevail?

The answers to such questions will largely depend, as the BMA recognises, on the perceived legitimacy of local bodies. For it is at the local level, if anywhere, that there is a democratic deficit in the NHS. Hence the BMA's proposal for elected local health councils. The notion may sound appealing, but it risks compounding the confusion of accountabilities in the NHS. Elected governors of foundation trusts are still in search of a role[8] and local authority committees are flexing their muscles,[9] all on top of a raft of patient involvement initiatives. The danger is that the NHS may become caught in a web of mechanisms, none of which is effective but all of which clog up policy and practice processes. Moreover, the question remains of how to make individual clinicians—who take crucial decisions about whom to treat and how—accountable for the decisions they make[10] without inhibiting professional discretion and introducing an extra layer of regulatory bureaucracy.

Whatever the reservations about the details of the BMA proposals, they have breathed fresh life and new ideas into an old debate in danger of going stale. Although the proposals can be criticised, it should be recognised that they pose an urgent challenge.

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Antipsychotic drugs in children with autism

Inadequacies in care should not be masked by the indiscriminate use of symptom controlling drugs

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The core problems of autism—those involving social interaction, communication, and restricted and repetitive activities—can be compounded by behavioural problems, including severe tempers, aggression, and irritability.[1] Severe aggression places a special burden on carers; it is more common in people with marked intellectual retardation and is related to poor daily living skills and impaired communication. Currently, no drugs are available to treat the underlying autistic condition. Specialised educational programmes, behaviour therapy, and environmental changes can improve aggressive behaviour,[1] but if they fail drug treatments should be considered.[2] Behavioural problems related to depression or attention deficit can be addressed by relevant therapy; but if the problem of aggression is unresponsive to these manoeuvres the need for symptom control arises. Major tranquillisers in particular have been used off-label, but their place has been uncertain because of doubts about safety and (until recently) efficacy.

Two well conducted double blind placebo controlled studies have compared placebo and the atypical antipsychotic risperidone in children with autism and behavioural problems. One study[3] included 101 children with diagnosed autism. The other[4] included 79 children with the broader category of "pervasive childhood developmental disorder," the largest subset (n=55) having autism. Both studies showed that risperidone significantly improved a mixture of behavioural problems, including aggression measured on the irritability subscale of the aberrant behaviour checklist.[5] This was accompanied by a global improvement as measured by the clinical global impression of change.

Adverse events were also reported such as somnolence (risperidone 67% *v* placebo 23%), extrapyramidal symptoms (risperidone 29% *v* placebo 10%), weight gain (risperidone 5% *v* placebo 0%), and raised prolactin concentrations (risperidone 43% *v* placebo 2%). Although prolactin concentrations tend to decrease with time, even while continuing risperidone, they are still higher than at baseline in longer term open label studies.[6] The effect of this on growth (including bone mineral density) and sexual maturation is not known.

The licence holder (Janssen-Cilag) for risperidone applied to the UK licensing authority, the Medicines

JULIE NICHOLS/SPL

and Healthcare Regulatory Agency (MHRA), to include irritability in autism as a licensed indication. Although efficacy had been demonstrated, there was concern about the potential misuse of this drug as a form of long term chemical control, especially of the most intellectually disabled children, who may be the most likely to have adverse effects. Thus, the Committee on Safety of Medicines sought the views of experts in child psychiatry, paediatric endocrinology, and pharmacokinetics and of medical centres that specialise in treating autism. The National Autistic Society was consulted, as well as parents of autistic children, who were asked about their child's perception of the drug as well as their own. The overwhelming view of both experts and service users was that, if used appropriately, antipsychotic drugs had a positive role in the management of aggression associated with autism. This resulted in the offer of a conditional approval limiting the use of risperidone to the symptomatic treatment of severe aggression and violence in children with autism.

The conditions included, as part of a risk management plan, safety monitoring through a newly established registry of children on treatment, with regular written reports to the MHRA. However, after considering the conditions of approval and following discussions with the MHRA, the company withdrew its application. Thus, an opportunity to establish a safer mechanism for screening and monitoring autistic children on risperidone was lost. In addition, there is a risk that a wider indication for behavioural disturbances in children with mental retardation may be gained in the United Kingdom via European procedures.

The Food and Drug Administration in the United States has taken a different view and has licensed risperidone for unrestricted use for irritability in children and adolescents with autism.[7] No limitations were put on the severity of the symptoms that might warrant risperidone and no restrictions were put in place, such as limiting prescription to experts in the field, although undertaking three further studies (two in animals and one clinical) was a condition of approval.

How should clinicians react? We consider that off-label use is still justified when other approaches fail or are unfeasible, and when underlying causes of aggression such as any physical condition or illness that causes distress to the child, adverse upbringing, or hyperkinetic disorder have been considered. These conditions are not contraindications to antipsychotic drugs, but attention to them may make medication unnecessary.

The assessment report on the use of risperidone in autistic children is available on the MHRA website.[6] It recommends a conservative approach—that this type of drug should be prescribed by experts in the treatment of autism who are prepared to undertake careful diagnosis, appropriate screening, and monitoring.

Diagnosis should distinguish between aggression and other seriously challenging behaviours (which may justify an antipsychotic agent) and lesser levels of "irritability" (which may not). Screening should uncover any physical problems causing behavioural problems, such as seizures, or remediable problems in the care environment, such as a lack of special measures to promote appropriate communication. Ideally, monitoring should include a pretreatment baseline period, and growth (height, weight, sexual maturation, evidence of gynaecomastia), behavioural change (somnolence, paradoxical exacerbation of behavioural problems), extrapyramidal symptoms, bowel habit, and blood pressure should be monitored. Routine invasive monitoring, such as blood testing, is not a condition of prescribing as it is often unacceptable to affected children, but if a child is more than 10 centile points above the expected weight, fasting blood glucose, lipids, and prolactin concentrations should be measured if possible. Urinary glucose testing may be done if blood tests are not practical.

Children with autism are among the most vulnerable in our society, and as such should not be deprived either of effective medication or of precautions to optimise safety. Historically, society has not offered these children the highest standards of care, and it is vitally important that inadequacies in care provision are not masked by the indiscriminate use of symptom controlling drugs.

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