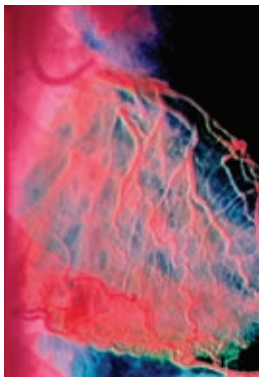
Coronary revascularisation

Surgery is effective on clinical and economic grounds, but stenting does not seem to be cost effective



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RESEARCH
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This week, the *BMJ* publishes three studies dealing with revascularisation in ischaemic heart disease.[1-3] Two of the studies compare the clinical effectiveness[1] and cost effectiveness[2] of revascularisation of isolated left anterior descending coronary disease by stenting or surgery, while the third examines the cost effectiveness of medical treatment, stenting, and surgery in multivessel disease.[3] The studies raise key issues not only about the decision making process for intervention in the individual patient but also how to obtain maximum value from limited health service resources.

Isolated left anterior descending coronary artery disease

Because the left anterior descending coronary artery supplies more myocardium than the circumflex or right coronary arteries, disease in its proximal portion carries a worse prognosis. When ischaemia is present, revascularisation improves survival[4] even in asymptomatic patients.[5] For more than two decades, the best option for revascularisation has been an internal mammary artery graft which, unlike vein grafts, is almost immune to the development of atherosclerosis.[6] This strategy significantly reduces the risk of death, subsequent myocardial infarction, recurrent angina, and the need for repeat intervention.[6] However, because surgery has conventionally required a median sternotomy incision and cardiopulmonary bypass, many cardiologists have favoured the less invasive option of percutaneous revascularisation with stents, unless contraindicated.

Two studies in this issue, one a systematic review and meta-analysis,[1] the other a cost effectiveness analysis,[2] report that internal mammary artery grafting using a less invasive surgical approach (through a small thoracotomy on the beating heart) is clinically at least as effective[1] and probably more cost effective[2] than stenting over the medium to long term. Compared with surgery, stenting resulted in an almost threefold increase in recurrent angina (odds ratio 2.62, 95% confidence interval 1.32 to 5.21) and an almost fourfold increase in the need for reintervention (4.63, 2.52 to 8.51).[1]

While mortality did not differ significantly between the interventions, the survival benefit of surgery may have been underestimated because follow-up was limited to less than four years in most of the studies (the survival benefit of surgery may not appear until later). Patients with severe and complex lesions that were not suitable for stenting were excluded from the trials, even though they would still have had a survival benefit with surgery.[4-6] Despite the findings, practice is unlikely to change as many patients with left anterior descending coronary artery disease—which is amenable to either intervention—may still favour the less invasive approach of stenting (even at a higher risk of reintervention) in the absence of a definitive survival advantage.

Multivessel coronary artery disease

Several trials of stents versus surgery in patients with multivessel coronary artery disease have reported no survival benefit from surgery. However, the trials randomised less than 5% of all potentially eligible patients and included only low risk patients. In effect, therefore, these trials were biased against the prognostic benefit of surgery in most patients with multivessel disease.[7] Consequently, these trials do not justify the widespread practice of inserting stents and deny some patients the survival advantage of surgery. Several large "real life" registries show that most patients with multivessel disease survive significantly longer after coronary artery bypass grafting rather than stenting,[8-10] and the benefit is even greater in patients with diabetes, who usually have more severe coronary artery disease.[11] For example, in the New York Registry database of almost 60 000 patients, after risk matching for cardiac and non-cardiac comorbidity, the three year mortality was 15.6% for stenting compared with 10.7% for coronary artery bypass grafting ($P<0.01$), and reintervention (35% *v* 5%) was seven times higher in patients receiving stents rather than surgery.[7] Nevertheless, despite the benefits of surgery on survival and freedom from reintervention, the number of stent procedures has increased dramatically in most industrialised countries in the past few years, so that this intervention now outnumbers surgery at least fourfold.

In contrast to the studies of the clinical effectiveness of surgery and stenting, the study by Griffin and colleagues[3] examines the cost effectiveness of medical treatment, stenting, and surgery in patients deemed suitable for each treatment by a panel of experts. It concludes that both medical treatment and surgery (but not stents) are cost effective at a conventional National Health Service quality adjusted life year threshold of £30 000 (€44 000; $58 000) and that the additional benefit of percutaneous coronary intervention over medical treatment is "too small to justify its additional costs."[3] While these findings are unlikely to be welcomed by the stent industry, valued at around $6bn each year, they echo the concerns of a previous report questioning the clinical

effectiveness and cost effectiveness of stents compared with medical or surgical treatment.[12]

Will the findings remain robust in the era of drug eluting stents?

The key to answering this question is based on understanding why surgery has a survival advantage over stents in multivessel disease.[8-10] Firstly, because bypass grafts are placed to the midcoronary vessels, surgery protects whole zones of vulnerable proximal myocardium against the "culprit" lesion (of any complexity) and against new lesions in diffusely diseased endothelium. In contrast, stents deal only with "suitable" culprit lesions and offer no protection against new disease. Secondly, the failure of stenting to achieve complete revascularisation in most patients with multivessel disease reduces survival proportional to the degree of incomplete revascularisation.[13]

For these reasons, even drug eluting stents are unlikely to match the results of surgery for most patients with multivessel disease. These same reasons probably explain the findings of several meta-analyses, which report that although drug eluting stents reduce the risk of restenosis in low risk coronary lesions, they do not reduce mortality or the risk of subsequent myocardial infarction.[14]

And disquiet about the lack of improved clinical outcome with drug eluting stents, despite their increased costs,[12] has recently been superseded by concerns about the increased risk of late thrombosis and its high associated mortality.[15] These clinical concerns are compounded by cost implications. Drug eluting stents cost more than bare metal stents, and new recommendations that patients remain on clopidogrel for at least a year[15] and possibly indefinitely will add greatly to costs.

Implications for health services and for patients

Griffin and colleagues highlight the tension between the adverse economic implications of the phenomenal growth in stent procedures and the absence of an appropriate evidence base to support such a policy. More importantly, this strategy has denied many patients with multivessel disease the prospect of a better long term outcome in terms of survival and freedom from reintervention offered by surgery. This highlights the dangers of individual practitioners rather than multidisciplinary teams making recommendations for stenting in patients with multivessel disease. Such teams should include a non-interventional cardiologist and surgeon and are likely to offer more balanced advice.[7] Griffin and colleagues have laid the challenge for "physicians, providers, and payers to prove that clinically appropriate treatments are also cost effective." To this we should add the challenge that a multidisciplinary approach should be a minimum mandatory "standard of care" to ensure that patients are offered the most clinically appropriate treatment.

Transparency in health technology assessments

Should NICE have the right to refuse access to its modelling data?

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The running battle over which National Health Service patients with dementia should have access to the dementia drug donepezil (Aricept) is to progress to the courts. Last year, guidance from the National Institute for Health and Clinical Excellence (NICE) restricted use of the drug to patients with moderate and severe Alzheimer's disease, thereby denying its use for 60% of patients with Alzheimer's disease who have mild dementia.[1]

NICE's decision was based on modelling Aricept's clinical and cost effectiveness through a contract with Southampton University's Health Technology Centre. NICE makes its own internal work accessible to the drug industry so that its processes are open to critical appraisal. Furthermore, it requires industry to supply all its evidence in an "executable" form, so that differing assumptions can be modelled. However, NICE's appraisal guide clearly states that the contracted work of external academic assessment groups will be available just in a "read only" form in which different modelling assumptions cannot be re-run.[2] NICE argues that this is essential to protect the intellectual property rights of assessment groups. This lack of transparency has never been challenged before, and although NICE's rules might be noble, protection of just this part of the assessment process may be unwise. However, with the resources at their disposal industry might be able to replicate the model from the read only version.

The drug company, Shire, in conjunction with the Japanese biotechnology company Eisai, which owns the licence for donepezil, have challenged the failure of NICE to provide access to the Southampton model in a judicial review.[3] NICE has expressed regret at the high opportunity cost of this challenge. It is determined to defend its position robustly.[4]

This conflict, and its narrow focus on the one area where NICE lacks transparency, may be an attempt by the drug industry to enhance its profits from a marginally cost effective drug. It might also be part of a more subtle drive to undermine processes of assessing health technology.

Australia has a similar system of assessing the cost effectiveness of drugs and devices and attempts have also been made to undermine its processes. The Australian Pharmaceutical Benefits Scheme was the first systematic attempt to develop health technology assessment to ensure that health systems adopt cost effective interventions. Its creation in 1993 was contentious for the drug industry, as the industry is a strong advocate of free trade, even though it is protected by patents and other regulatory devices that enhance monopoly power and profits. Some academics and former committee members of the Pharmaceutical Benefits Scheme fear

that it will be undermined by pressure from the United States. For instance, negotiations over the 2005 free trade agreement between the US and Australia focused on removing regulatory barriers to trade such as technology appraisal epitomised by the Pharmaceutical Benefits Scheme.[5] The US government is arguing that technology appraisal, such as that in the Australian Pharmaceutical Benefits Scheme, creates obstacles to the free trading of drugs as it bars some products from reimbursement and affects their "free market" price to the detriment of producers. The recent visit to the United Kingdom of the US deputy secretary for health has raised similar concerns in the UK. Mr Azar was quoted as saying that "mechanisms such as those of NICE for rationing drugs to keep costs down stifle innovation," and concern was expressed that this was part of the efforts of drug companies "to have unrestricted access to the NHS as part of a free market."[6]

The work of NICE is essential for resources to be targeted towards patients who will benefit the most. Generally its processes are transparent and sensible. However, the constraints under which it works can be improved.

Firstly, NICE has to accept the product prices set by industry and is unable to bargain them down to more reasonable levels that might facilitate acceptance and use by the NHS. Price setting is influenced by the Pharmaceutical Price Regulation Scheme, which allows industry to set prices and protect target profit levels of 17-21% return on capital. The Office of Fair Trading has criticised the Pharmaceutical Price Regulation Scheme and advocated pricing in relation to "economic value."[7] Calculation of economic value may deflate future drug prices, and if NICE were given this role the need for transparency in its decision making would be important.

While NICE may estimate the financial consequences on the NHS of its guidance, it is assumed that primary care trusts can fund all its guidance. This is incorrect as implementation will be uneven and produce new forms of postcode rationing.[8] Also, NICE guidance is increasing as the growth of NHS funding is declining. In setting NICE's work agenda, ministers need to prioritise removing inefficient technologies rather than adding new technologies to the NHS.[9]

NICE is an essential institution for improving the efficiency of the NHS. It will never be perfect because evidence from clinical trials and economic modelling may be corrupted by poor science in the practice of clinical and economic evaluation.[10-12] This makes transparency essential.

With the NHS seeking to control expenditure and target the use of drugs to improve the health of the population in a cost effective manner, and industry wanting to maximise its profits, conflict is inevitable. The trade-off between health and wealth should be managed with transparent and good science by all participants—both public and private.

Global health partnerships

Changes to training and revalidation may impede the UK's support of health care in developing countries

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The *Global Health Partnerships* report by Lord Crisp,[1] commissioned by the prime minister, aims to find ways to strengthen the United Kingdom's contribution to health care in developing countries. The report acknowledges the UK's "remarkable intellectual and practical leadership in international development" and recommends that the UK facilitate and support the "very valuable work already being done by so many UK organisations and individuals." The report goes on to describe the potential benefits of such activities both to developing countries and to the individuals involved.

Warm words are welcome, especially when backed up by practical measures. Lord Crisp makes excellent recommendations for new departures, ranging from explicit ministerial support for National Health Service staff to spend time working in developing countries, to making it easier for aid workers to maintain NHS pension contributions. However, recent changes to the NHS are making it more difficult for UK medical staff to engage positively in three important areas. Lord Crisp notes all three, if occasionally indirectly; unless rapid action is taken these changes will erect new barriers to the UK supporting health care in developing countries.

The first area is allowing medical staff in developing countries to undertake higher training in the UK. Recent changes in immigration policy and their probable impact have been widely discussed, but it is worth noting that Lord Crisp repeatedly found that doctors in developing countries wished to undertake some specialist training in the UK. Finding mechanisms to achieve this without stripping developing countries of medical staff should be possible, but it is getting more difficult.

The second area is revalidation. Doctors from the UK undertake work in developing countries in a variety of ways, but most of them wish to practice in the UK afterwards. Such overseas work includes repeated short term deployment in emergencies or longer term deployment in complex emergencies with non-governmental organisations; medium or long term periods providing medical services or training medical staff; and periods of often many years spent undertaking research in the tropics. The General Medical Council has tried to be flexible in designing ways to allow doctors doing overseas work in these varied work patterns to undertake revalidation, or to relinquish but then regain the licence to practise with minimum bureaucracy and maximum speed. It is essential that this flexibility survives the recent white paper on revalidation.[2] In his initial report[3] and foreword to the current proposals, the chief medical officer stated that humanitarian work by NHS staff should not be

disadvantaged by the new system, but this does not seem to have been taken into account of in the government's subsequent proposals.

The greatest threat to the ability of UK doctors to undertake work in the developing world, however, is the modernising medical careers (MMC) initiative. Those who designed this initiative did not intend to make it difficult for doctors in training in the UK to work in the developing world, but that is what they have done. This is disappointing as the Department of Health is simultaneously stating how important our engagement in global health is for the UK, and that joined-up government is the key to this, most recently in a major report released by the chief medical officer.[4] Lord Crisp states that "the introduction of MMC could provide the opportunity to reconsider how international medical training and overseas work might be included in the higher medical training posts both in the foundation years and within specialist training." This is an aspiration all would support, but the immediate priority is to prevent MMC destroying what already exists. Currently, most UK doctors who go on to spend some of their career working in the developing world get their first experience at the senior house officer stage. If they go earlier they have too few skills to be of use to their host country, but later on most are already embarked on medical specialisation. The current model of MMC makes a break from the career pathway at this point extremely difficult.

We need to match the warm words about the importance of assisting the developing world with a serious attempt to build flexibility into the MMC, revalidation, and licensing structures to allow the varied patterns of work that are needed for short term work in humanitarian non-governmental organisations, spells of teaching or medical service, and medical research of varying lengths. If this does not happen doctors will be able to choose to train in the NHS, or to assist the developing world, but not both. This would be a great shame. As Lord Crisp points out, currently the UK has much to be proud of in this area, and it would be a tragedy to destroy it by accident. He recommends that the Postgraduate Medical Education and Training Board, deaneries, and the royal colleges need to take action. The need to do so is even more urgent than he implies.

New mental health legislation

A decade's deliberations result in confused proposals

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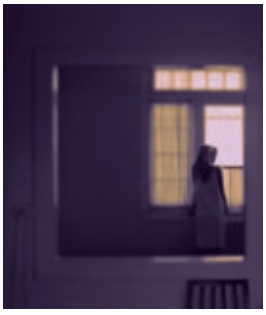

Why after 10 years' effort has the latest Mental Health Bill published in November 2006 been damned as "stigmatising, illiberal and yet curiously timid … a little like a dying wasp which still has a sting in it"? In November 1999, the Richardson Committee [2] reported on the reform of mental health law in England and Wales. Patients' rights would be safeguarded by balancing guiding principles and the adoption of capacity—the legal ability to make decisions about treatment—as a determinant of whether compulsory detention and treatment should take place. New law mirroring these key proposals has been successfully introduced in Scotland,[3] but in England and Wales the path to reform has been tortuous (table).

The current bill[4] bears little resemblance to the proposals set out by the Richardson Committee. There is provision, as in Scotland, for supervised treatment in the community, but without the safeguards found in the Scottish act. Certain exclusions to compulsory detentions are removed: promiscuity, immoral conduct, and sexual deviance. Whereas the government sees the first two exclusions as redundant, they identify the third as a category for which compulsory treatment should be expanded. The bill positively endorses the compulsory treatment of people with sexual disorders such a paedophilia.[5] The only remaining conditions to be excluded are drug and alcohol misuse.

The professional background of who has the authority to be responsible medical officer and mental health officer for detained patients is to be widened to include psychologists, occupational therapists, and nurses. In the case of primary personality disorders, psychologists are identified as being particularly suitable to be the "responsible clinicians" in charge of patients, but the bill is unclear how this would work in practice. Medical practitioners are still required to instigate detention, but a wider group would be responsible for renewal of detention and ongoing monitoring.

There will also be a change to the treatability test, which states that for someone to be detained under the category of psychopathic disorder, treatment must alleviate or prevent a deterioration in the condition. Before the bill was introduced, this test was perceived as limiting the detainability of certain patients with personality disorder. The test will be replaced by a broader "appropriate treatment test," which will make patients with a psychopathic disorder detainable if appropriate treatment exists. The only new safeguard to patients in the bill is the amendment of legislation to restore the Mental Health Act's compliance with human rights after an adverse decision by the European Court on the Bournewood case.[6] In this case an autistic man, who was unable to consent, was admitted to hospital informally and was not detained, which left his carers no legal structure to challenge the appropriateness of the admission. The European Court ruled that in these circumstances he should have been detained to afford him and his carers a legal structure to defend his human rights.

The fundamental flaw in the proposed legislation, as it was in the two preceding unsuccessful bills, is the government's belief that mental health law is a worthy vehicle to enhance public protection—a belief that has been extensively criticised.[7] Legislation in Scotland has

Development of mental health law proposals in England and Wales

Date	Event
1998 to 1999	Richardson Committee reported November 1999
1999	Managing dangerous people with severe personality disorder: proposals for consultation; proposed by the Department of Health and Social Security, Home Office, and Welsh Office
November 1999	Government green paper: reforming the Mental Health Act 1983
December 2000	Government white paper: reforming the Mental Health Act 1983
June 2002	Draft mental health bill
September 2004	Second draft bill
November 2004 to March 2005	Scrutiny by Joint Committee of parliament concluded the plans were "fundamentally flawed"
July 2005	Government response to Joint Committee rejecting its key recommendations
November 2005	Race equality impact assessment on the bill
23 March 2006	Government abandons mental health bill
17 November 2006	New mental health bill published

been successfully implemented because the Scottish Executive followed the advice of its expert group and that of wide consultation by keeping the focus of mental health legislation on care and treatment.

The paradox is that an overemphasis on public safety in mental health law increases risk to the public. The widening definition of mental disorder and treatability will place most prisoners within the ambit of compulsory psychiatric treatment. What prisoner will engage in an anger management course or a sex offender programme with the prospect of compulsory indefinite detention and transfer to a secure psychiatric hospital? What potential patient with a violent thought will dare seek help from a doctor? Medicalising violent and sexual offenders is unlikely to reduce relapse into criminal behaviour unless the aim is very lengthy preventative detention.

The problem of violence in the mentally disordered is much more about how society manages violence generically than how it manages mental disorder. The rate of violence in people with mental disorder mirrors the rate of violence in the societal group they come from.[8] The association between mental illness and serious violence is modest and easily obscured by weightier predictors of crime.[9] Mental health services concentrate on serious mental illness, yet the proposed legislation is so broad that it potentially includes most violent offenders. The best way for mental health to protect the public is the provision of comprehensive services, but there needs to be a realistic appraisal of what can be offered. This was summed up by Nigel Eastman in his evidence to the Joint Scrutiny Committee of parliament on the marginal contribution psychiatry can make to public protection. He said, "It is not that you can predict if somebody is going to kill somebody; it is that you intervene for their mental health care, and one out of goodness knows how many would have gone on to kill but you have intervened."[10]

The bill's proposers have been too sensitive to individual high profile tragedies. Yet inquiries into homicide committed by people in recent contact with mental health services rarely comment on a deficiency of law in their recommendations. Politicians and the media may highlight that one homicide a week is perpetrated by someone with a mental illness[11] and the failings in mental health care associated with the manslaughter of Denis Finnegan by John Barrett.[12] However, evidence that any of these tragedies would have been prevented by a change in mental health law is lacking. Results from the National Confidential Inquiry identified only 12 cases, 6% of a sample, where respondents involved in the care of a mentally ill perpetrator believed different legal powers may have made a homicide less likely.[11] The rate of homicide associated with mental illness has not been affected by earlier changes in the law or the introduction of community care—the proportion of homicides perpetrated by those with mental illness has changed little during the past 50 years.[13] Psychiatry aims to increase autonomy not to force a competent patient always to choose what is right.

New mental health legislation in England and Wales has faltered because of a confusion of purpose. The Mental Health Alliance is a remarkable coalition of interested parties, which correctly focuses the need for legislation on the care of patients.[14] Where mental disorder does not reduce the ability to make moral choices it is not for mental health legislation to intervene. Criminal justice agencies and legislation should lead in the case of a personality disordered or sexually deviant offender, appropriately supported by mental health services. Efforts for reform will fail if mental health legislation is wrongly identified as a principal mechanism for enhancing public safety.

Urinary tract infection in primary care

First line treatment should be informed by clinical and microbiological data

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A recent prospective cohort study by McNulty and colleagues in the *Journal of Antimicrobial Chemotherapy* reports on 448 women with symptoms of uncomplicated urinary tract infection who were treated with trimethoprim in primary care.[1] The aim was to see whether women with infections resistant to trimethoprim had worse clinical outcomes. While the answer might seem intuitive, some of the findings were interesting. Pure bacterial culture was found in 317 women and the rate of resistance to trimethoprim was lower than expected from local laboratory resistance data derived from routinely collected specimens (13.9% *v* 24.5-27%). Predictably, antibiotic resistance was associated with longer median duration of symptoms (7 *v* 4 days; P<0.0002), higher frequency of subsequent prescription of antibiotics (36% *v* 4% in the first week; P<0.0001), and higher rates of reconsultation for treatment failure (39% *v* 6%; P<0.0001). While this sixfold relative difference in treatment failure rates is impressive, what is interesting from a primary care perspective


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is the low absolute reconsultation rate in the subsequent week in the resistant group (39%). In other words 61% of women with resistant organisms did not reconsult in the subsequent week because of treatment failure.

The treatment of uncomplicated urinary tract infection in primary care is usually empirical. The decision about which antibiotic to use may be influenced by both the practitioner's and the patient's previous experience, available data on antibiotic sensitivities, guidelines, and drug marketing.[2] General practitioners face two sometimes competing imperatives—the first to choose an effective treatment for the individual and the second to minimise resistance in the population by using antibiotics responsibly.

Data on local resistance are generally derived from routine clinical specimens being processed by community or hospital laboratories. Many sources of bias may exist in these data relating to referral patterns and pooling of results by organism rather than clinical condition. This bias results in overestimation of resistance rates in women with symptoms of uncomplicated urinary tract infections.[3-7] The findings in this UK study concur with this—13.9% of patients in the study were resistant to trimethroprim compared with 24.5-27% in routinely collected specimens.[1]

The authors call for more systematic and regular surveillance, which puts data into the prescribing context. Without such data, overestimations may influence prescribers to change their first line prescribing choices earlier than needed, especially if reinforced by drug companies promoting newer agents.

Ultimately, it is relief of symptoms that matters to patients, not microbiological eradication. We therefore need to use data on resistance with care when making decisions and developing guidelines for prescribing in primary care.

The British Society for Antimicrobial Therapy and US Clinical and Laboratory Standards Institute breakpoints (the minimum inhibitory concentration (MIC) standard in vitro that determines whether an organism is classified as "resistant" or "sensitive") for determining resistance are best estimates of clinically important resistance. These are usually based on anticipated responses in bloodstream infections using pharmacodynamic, microbiological, and, where available, clinical response data. Many factors influence clinical outcome, including variable relations between concentrations of antibiotics in the blood and urine and patient characteristics.

The microbiologically determined resistance rates found by McNulty and colleagues might prompt a general practitioner to assume that a resistance rate of 13.9% equates to a similar treatment failure rate. If this were so, the number needed to investigate to change clinical outcome would be 10 (44/448). When reconsultation because of treatment failure due to resistance is the main outcome, the number needed to investigate rises to 26 to prevent reconsultation in the next week and 23 for the next month (20/448).[1] The same may be true for other antibiotics used to treat urinary tract infections.[8-9] There may be wider lessons here about using intermediate outcome indicators like antibiotic resistance to guide prescribing decisions in general practice. Similarly, urine dipstick testing predicts significant bacteriuria but does not reliably predict response to antibiotic treatment.[10] Taking a broader view, the limitations of risk factors as prognostic tools have recently been highlighted, as risk factors do not necessarily predict development of disease.[11]

The authors claim that their data support trimethoprim as an appropriate first line agent for uncomplicated urinary tract infection in their region. It is clinically effective, relatively safe, and inexpensive. Trimethoprim is alone in its class, which reduces the likelihood of resistance selection to other, newer antibiotics, and it is rarely, if ever, used for more serious infections. We agree with the authors' conclusions that the decision to switch to a second antibiotic should be made on clinical grounds rather than on microbiological grounds—that is, failure of symptoms to resolve after four days of treatment. With a clinical failure rate of 17/448, general practitioners can confidently tell patients that most women's symptoms will resolve quickly, and that they should return if symptoms are not improving by four days—sooner if symptoms worsen. Laboratory investigation seems warranted only if initial treatment fails.

The relation between laboratory determined and clinical resistance will not be constant, or necessarily generalisable from this study. It follows that choice of first line treatment should be informed by periodic and systematic community surveillance using clinical and laboratory defined outcomes. This is likely to be cheaper overall than routinely ordering pretreatment investigations that are unlikely to be helpful for empirical prescription and may lead to unnecessary second prescriptions.

Many questions still need to be answered. Just as the relation between prescribing patterns, resistance, and clinical outcomes is complex,[12] the association between detectable infection and response to antibiotics is not linear.[10] Ironically, rigid prescribing guidelines for first line treatment may be less helpful in containing antibiotic resistance. It has been suggested that (rational) diversity of first line agent may dilute selection pressure, and further evaluation of a variety of strategies is needed.[12] We do not know why some people with symptoms respond to antibiotics faster than to placebo when they do not have infection by any accepted definition, while others with sensitive organisms fail to respond to antibiotics.