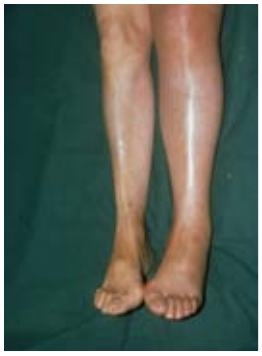
Antipsychotics and the risk of venous thromboembolism

A higher risk—so treatment should be tailored according to individual risk factors



ST BARTHOLOMEW'S HOSPITAL/SPL

RESEARCH, p 641

Rosa Liperoti specialist in geriatrics
rosella_liperoti@rm.unicatt.it
Giovanni Gambassi professor of geriatrics, Centro di Medicina dell'Invecchiamento, Dipartimento di Scienze Gerontologiche, Geriatriche e Fisiatriche, Università Cattolica del Sacro Cuore, Largo A Gemelli 8, 00168, Rome, Italy

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2010;341:c4216
doi: 10.1136/bmj.c4216

Patients with schizophrenia have an increased risk of venous thromboembolism (VTE), and this might be associated with the use of antipsychotics, especially low potency drugs such as chlorpromazine and thioridazine.[1] Among atypical antipsychotics, clozapine has consistently been associated with VTE in young patients with psychiatric illnesses,[2] but evidence from large observational studies has suggested that other atypical antipsychotics carry a similar risk, especially among new users and elderly patients.[3] So far, however, the possibility that the underlying psychiatric disorders themselves—and not the antipsychotics—are associated with VTE has never been excluded. This could occur, for example, by the increased concentrations of adrenaline seen during psychotic excitation increasing blood coagulation.[4]

In the linked study, Parker and colleagues report a large population based case-control study that included primary care patients aged over 16 who were taking antipsychotics.[5] In almost 99% of cases the reason for prescription of antipsychotics could not be ascertained. Most antipsychotics used were conventional agents, with prochlorperazine—probably given for nausea and vomiting—accounting for almost 80% of all prescriptions. The authors found that the use of antipsychotics was associated with a significantly increased risk of VTE (odds ratio 1.32, 95% CI 1.23 to 1.42). The validity of the findings is strengthened by the large sample size and the low potential for exposure and outcome misclassification because of the detailed source of data and adjustment for a large number of confounders.

The highest risks were for quetiapine (nearly fourfold increased risk) and for low potency antipsychotics rather than high potency ones. New users of antipsychotics seemed at greater risk than continuing users, and the effect was not seen in those who stopped taking the drug. These findings indicate that VTE is directly linked to the use of an antipsychotic, and that the risk of VTE increases early after starting the drug.

The mechanisms by which antipsychotics contribute to VTE remain elusive. Venous stasis can be exacerbated by excessive sedation.[1] The metabolic abnormalities (dyslipidaemia, increased plasma concentrations of leptin and glucose, hyperhomocysteinaemia, and weight gain) documented especially among users of atypical antipsychotics may be associated with decreased fibrinolytic activity,[6] but they take months or years to manifest and occur only in long term users. Patients on conventional antipsychotics and clozapine have shown high levels of circulating lupus anticoagulant and anticardiolipin antibodies, but these are seldom associated with thromboembolism.[7]

Changes in platelet function, plasma coagulation, or fibrinolysis are likely to be responsible for the increase in thrombotic events because VTE occurred early and during treatment of short duration; in addition, the risk of VTE was higher when antipsychotics were injected. Conventional agents, including chlorpromazine, fluphenazine, flupentixol, trifluoperazine, and haloperidol, have been associated with enhanced aggregation of platelets.[8] Inhibition of 5-hydroxytryptamine 2A platelet receptors by clozapine, olanzapine, and risperidone can modulate receptor density and affinity but does not uniformly enhance platelet adhesion and aggregation.[9] An effect of antipsychotics on platelets is supported by recent experimental findings.[10]

Although VTE is treatable it has a three month mortality rate of 15-18%,[11] and evidence is accumulating that the use of antipsychotics is an established risk factor for VTE. However, consistent with previous estimates, Parker and colleagues found a low absolute risk of antipsychotic related VTE (four extra cases of VTE per 10 000 patients treated over one year), and doctors should consider this risk when making clinical decisions. The rarity of such adverse events does not justify antithrombotic prophylaxis for patients on antipsychotics without other medical conditions for which such preventive treatment is indicated.

Despite their association with serious risks and few data to support their efficacy antipsychotics are widely used, and in 2008 they became the top selling drug class in the United States, ahead of lipid regulators and proton pump inhibitors.[12] Despite efforts to improve non-drug based interventions, antipsychotics are often used, especially for the treatment of agitation in people with dementia.

In clinical practice we need to be able to identify the best candidates for antipsychotic treatment, such as those people with the lowest vascular risk profile who may respond to short term and low dose treatment with antipsychotics because of individual pharmacogenetic characteristics, and those who may be more susceptible to developing side effects as a result of individual vascular risk factors possibly interacting with antipsychotics.

1 Hägg S, Jönsson AK, Spigset O. Risk of venous thromboembolism due to antipsychotic drug therapy. *Expert Opin Drug Saf* 2009;8:537-47.
2 Paciullo CA. Evaluating the association between clozapine and venous thromboembolism. *Am J Health Syst Pharm* 2008;65:1825-9.
3 Jönsson AK, Horváth-Puhó E, Hägg S, Pedersen L, Sørensen HT. Antipsychotics and risk of venous thromboembolism: a population-based case-control study. *Clin Epidemiol* 2009;1:19-26.
4 Hindersin P, Siegmund R, Körting HJ. Thrombophilic diatheses as hemostasis disorders in acute psychoses. *Psychiatr Neurol Med Psychol (Leipz)* 1984;36:702-9.
5 Parker C, Coupland C, Hippisley-Cox J. Antipsychotic drugs and the risk of venous thromboembolism: nested case-control study. *BMJ* 2010;341:c4245.
6 Chaggar PS, Shaw SM, Williams SG. Effect of antipsychotic medications on glucose and lipid levels. *J Clin Pharmacol* 2010 published online 21 April.
7 Canoso RT, de Oliveira RM, Nixon RA. Neuroleptic-associated autoantibodies. A prevalence study. *Biol Psychiatry* 1990;27:863-70.

8 Orr MW, Knox JM, Allen R, Gelder MG, Grahame-Smith DG. The effects of neuroleptic drugs on 5-hydroxytryptamine induced platelet aggregation in schizophrenic patients. *Br J Clin Pharmacol* 1981;11:255-9.
9 Axelsson S, Hagg S, Eriksson AC, Lindhal TL, Whiss PA. In vitro effects of antipsychotics on human platelet adhesion and aggregation and plasma coagulation. *Clin Exp Pharmacol Physiol* 2007;34:775-80.
10 Oruch R, Hodneland E, Pryme IF, Holmsen H. In thrombin stimulated human platelets citalopram, promethazine, risperidone, and ziprasidone, but not diazepam, may exert their pharmacological effect through intercalation in membrane phospholipids in a receptor-independent manner. *J Chem Biol* 2009;2:89-103.
11 Tapson VF. Acute pulmonary embolism. *N Engl J Med* 2008;358:1037-52.
12 Kuehn BM. Questionable antipsychotic prescribing remains common, despite serious risks. *JAMA* 2010;303:1582-4.

Is it time to revisit orphan drug policies?

Yes, for equity's sake

RESEARCH, p 642

Christopher McCabe professor of health economics, Academic Unit of Health Economics, Leeds Institute of Health Sciences, University of Leeds, Leeds LS2 9LJ, UK
c.mccabe@leeds.ac.uk
Tania Stafinski associate director health technology and policy unit
Devidas Menon professor of health policy and management, Department of Public Health Sciences, School of Public Health, University of Alberta, Edmonton, AB Canada T6G 2V2

Cite this as: *BMJ* 2010;341:c4777
doi: 10.1136/bmj.c4777

The number of new treatments for rare disorders—so called orphan drugs—has increased over the past decade. This is a testament to the success of the Orphan Drug Act in the United States and the Orphan Drugs Regulation in Europe.[1 2] The large number of treatments in late stage development indicates that this success is likely to be sustained.[3] However, this poses a substantial challenge for healthcare systems because the prices charged for these drugs make it impossible for them to meet conventional measures of good value.[4] Increasingly, access to orphan drugs is likely to be restricted, causing political problems for governments and reducing the return to manufacturers from their research investment.

To date, many healthcare payers have exempted orphan drugs from formal value assessment, arguing that society values equal opportunity for people with rare and common conditions enough to justify the high costs. Until now this has been assumed, rather than being based on robust evidence.[5]

In the linked survey, Desser and colleagues asked a representative sample of the Norwegian general population whether society should pay more to treat rare diseases than it does for common diseases.[6] They found that although respondents supported equality of access to health care for people with rare diseases they did not support providing care for people with rare diseases when the cost of that care was at the expense of people with common conditions. The implication from this study is that funding policies that take resources from the national healthcare budget to fund these treatments are not what the public wants.

Desser and colleagues' study mirrors results emerging from two citizens' juries held in Canada. After two and a half days of deliberation, the juries opted to take a health maximisation approach, most readily achieved by providing a sufficiently effective intervention to the largest number of patients. A preference for treating small numbers of patients was expressed only if the patients were severely ill and the treatment could produce substantial health gain to all of them, bringing them back to normal functioning. Relatively few patients with orphan conditions would meet these criteria.

The current model of developing and funding orphan drugs is not fit for purpose if it cannot deliver treatments at a price that healthcare systems can afford. In the short term, modifications to the system may help contain the excess health burden of funding orphan drugs. For example, drugs with multiple indications, such as imatinib and sildenafil, could be excluded from special funding schemes because the return on the investment is made by patients with non-orphan diseases receiving the drug. In addition, changes in clinical practice that would optimise cost effectiveness, rather than clinical effectiveness, might help. For example, doses of enzyme replacement therapy aimed at improving clinical outcomes rather than achieving biochemical targets might be more cost effective and affordable.[7] Finally, the commercial attractiveness of the orphan drugs market, as shown by major drug companies' moves to enter the market, suggests that there is room for more aggressive price negotiation.[8]

In the long term, a fundamental change in the funding model will probably be needed, and lessons might be learnt from the strategies adopted for neglected diseases in resource poor countries. The high level of uncertainty about the sustainability of demand for new products is similar for orphan diseases and neglected diseases.

New treatments for neglected diseases are being developed through product development partnerships that bring together civil society (represented by academia), the public sector (government), and the private sector.[9] These partnerships achieve superior development timelines and greater cost efficiency than purely public or private endeavours. As these technologies have moved to the later stages of development, advanced market commitments are being used to create a market of sufficient value to stimulate research, development, and the manufacture of new drugs. Advanced market commitments provide industry with the security of demand needed to invest in manufacturing capacity and healthcare systems and the security of supply needed to plan the large scale introduction of new technologies.

The parallel between the challenges of developing and implementing treatments for neglected diseases in developing countries and treatments for orphan diseases in developed countries is increasingly strong; the question is whether the solutions developed for neglected diseases can be adapted for orphan diseases.

Decision makers will probably be reluctant to take up the fiscal challenge of orphan drugs. Each orphan drug treats a small number of individuals. Each individual provides a persuasive human story that supports funding treatment. Experience has shown the power of individual stories in healthcare funding debates.[10-12] However, if decision makers wish to act on society's values, Desser and colleagues' results indicate that they will need to make hard choices to ensure that the anonymous many are not harmed to benefit the identifiable few.

Competing interests: In the past three years CMcC has served on advisory boards for Celgene and GlaxoSmithKline, which manufacture orphan drugs; CMcC serves as a scientific adviser to the Biotherapies Development Association, which promotes academic and policy debate around access to oncology treatments including orphan drugs, receives funding from pharmaceutical companies, and has met CMcC's expenses for attending three workshops; DM has received non-personal funding from the Canadian

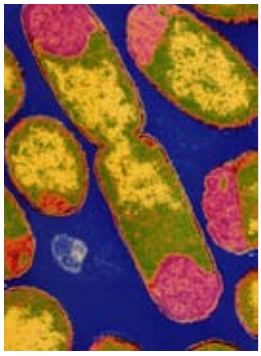
Institutes for Health Research to examine the role of social preferences in health care resource allocation processes; TS received an honorarium for helping to run a workshop organised by the Canadian Association for Rare Disorders; none of the authors have non-financial interests that may be relevant to the submitted work.

Provenance and peer review: Commissioned; not externally peer reviewed.

1 US Food and Drug Administration. Orphan drug act (as amended). www.fda.gov/orphan/oda.htm.
2 Regulation (EC) No 141/2000 of the European Parliament and of the Council of December 16, 1999 on orphan medicinal products. *Official Journal of the European Communities* 2000;43(L18):1-5.
3 Miles KA, Packer C, Stevens A. Quantifying emerging drugs for rare conditions. *QJM* 2007;100:291-5.
4 Drummond MF, Wilson DA, Kanavos P, Ubel P, Rovira J. Assessing the economic challenges posed by orphan drugs. *Int J Technol Assess Health Care* 2007;23:36-42.
5 National Institute for Health and Clinical Excellence. Citizens council. Report on ultra-orphan drugs. 2004. www.nice.org.uk/niceMedia/pdf/Citizens_Council_Ultraorphan.pdf.
6 Desser AS, Gyrd-Hansen D, Olsen JA, Grepperud S, Kristiansen IS. Societal views on orphan drugs: cross sectional survey of Norwegians aged 40 to 67. *BMJ* 2010;341:c4715.
7 Department of Health. Guidelines for the management of paediatric Gaucher disease. 2005. www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4118411.pdf.
8 GenEngNews. Big pharma steps into orphan drugs market. 2010. www.genengnews.com/gen-articles/big-pharma-steps-into-orphan-drug-market/3329.
9 Grace C. Developing new technologies to address neglected diseases: the role of product development partnerships and advanced marked commitments. DFID Health Resource Centre, 2006. www.dfidhealthrc.org/publications/PDPs_and_AMCs_presentation_06.pdf.
10 Thomas H. Fighting for herceptin. BBC Stoke and Staffordshire, 2005. www.bbc.co.uk/stoke/content/articles/2005/09/26/herceptin_intro_2005_feature.shtml.
11 BBC News. Woman denied "sight-save drugs". 2008. http://news.bbc.co.uk/1/hi/england/london/7288326.stm.
12 Osley R. Condemned to die...the patients being refused a life-saving cancer treatment drug. *Camden New Journal*, 2007. www.thecnj.com/camden/2007/101807/news101807_09.html.

Globalisation and antibiotic resistance

Hospitals engaged in medical tourism can turn crisis into opportunity



A B DOWSETT/SPL

Anthony So director, program on global health and technology access
anthony.so@duke.edu
Melissa Furlong associate in research, Sanford School of Public Policy and Duke Global Health Institute, Duke University, Durham, NC 27708, USA
Andreas Heddini executive director of ReAct (action on antibiotic resistance), Department of Medical Sciences, Uppsala University, Uppsala, Sweden

Cite this as: *BMJ* 2010;341:c5116
doi: 10.1136/bmj.c5116

The global spread of bacteria carrying the New Delhi metallo-β-lactamase-1 (NDM-1) enzyme through India, Pakistan, and the United Kingdom—and now half a dozen other countries—has sparked much media coverage.[1] The outbreak's importance stems from the broad resistance to all antibiotics except tigecycline and colistin seen in bacterial strains carrying the gene for NDM-1 and from the ready transmission across borders.

The original report of NDM-1 cautioned against medical tourism, suggesting the costs of contracting treatment resistant infection outside the UK might well outweigh the savings of lower priced care abroad. The naming of NDM-1 after New Delhi—its purported place of discovery—further vexed Indian government officials worried about potential fallout for the country's burgeoning medical tourism industry. This added drama has distracted attention from what ought to be the main plot of this story.

Modern advances in health care, from organ transplants to cancer chemotherapy, are reliant on effective antibiotics and vulnerable to resistance. Multidrug resistant strains are no longer an isolated phenomenon, nor confined by political borders. To India's credit, the government is preparing a policy on rational use of antibiotics.[2] Healthcare leaders gather on 22 September 2010 for the World Medical Tourism and Global Healthcare Congress in Los Angeles, and these topics ought to be on their agenda.

Restricting medical tourism will not result in effective quarantine. Foreign travel alone resulted in healthy Swedish volunteers becoming colonised with extended spectrum β-lactamase-producing bacteria.[3] Nor are outbreaks of resistant strains limited to hospitals in low income and middle income countries. Meticillin-resistant *Staphylococcus aureus* (MRSA) was first reported in the UK in the 1960s and has since spread worldwide.[4] Antibiotic use and resistance levels vary widely even among countries in the European Union.[5]

With a dearth of novel antibiotics in the pipeline, the conservation of existing ones is imperative. Infection control and rational antibiotic use are central to such efforts, but it is also susceptible to the failure of collective action. No hospital can remain an island if other community institutions are not doing their part in infection control.[6] The spread of NDM-1 also suggests that globalisation has redefined the bounds of community. To tackle antibiotic resistance, all involved must "think globally, act locally."

Hospitals engaged in medical tourism can make a difference. These institutions seek to deliver the latest in medical advances to patients. In 2007, 750 000 Americans travelled abroad for treatment, and 417 000 non-citizens came to the United States seeking medical care. By 2012, the global market for medical tourism is projected to rise to $100bn (£63.8bn; €76.1bn).[7] Delivering high quality care depends on keeping antibiotic resistance in abeyance.

Hospitals engaged in medical tourism are often beacons of quality care in their local healthcare systems. However, in otherwise resource-limited settings, these hospitals can present concerns of health inequity, where patients who can pay receive the best of care, but others just outside their doorsteps cannot. This is, of course, still true in the United States, even after recent healthcare reforms. But such hospitals are particularly well positioned to show leadership in reducing the spread of resistant pathogens.

Increasingly, accreditation organisations like Joint Commission International work with institutions seeking globally recognisable certification on quality measures like infection control. In 2007 only 125 hospitals were accredited by Joint Commission International,[8] but that number has increased to nearly 300 in 2010. How can the system move from standards to stewardship?

Prescriber education, formulary restriction and preauthorisation, and surveillance strategies are among the components that comprise a programme for antimicrobial stewardship.[9] Viewed from a health system's perspective, how can economic incentives be aligned to support infection control at the individual hospital level? Where healthcare infrastructure is limited, how might infection control differ from measures taken in better resourced hospitals? The Ashoka Changemakers competitions bring together communities to collaborate and to reward and encourage end user innovation. In the same crowdsourcing spirit, novel approaches for infection control might be discovered and piloted.

Hospitals engaged in medical tourism can lead by example. These institutions could pledge to a process to improve infection control and to measure performance for accountability.[10] Such efforts in relation to coronary artery bypass graft surgery have led to the voluntary reporting of risk adjusted outcomes in an online report card.[11]

How can institutional commitments translate into collective action? The World Health Organization's World Alliance for Patient Safety and the Institute for Healthcare Improvement's 5 Million Lives Campaign offer some lessons. Eight hospitals in different countries used a shared surgical safety checklist and lowered death rates and complications as part of the WHO's Safe Surgery Saves Lives campaign.[12] The 5 Million Lives Campaign enlisted more than 4000 hospitals in the United States to undertake interventions to minimise medical harms. The campaign developed a methodological approach to track progress, including the use of triggers to identify adverse events. A system of monitoring will help ensure that accountability will follow commitment. From reducing MRSA infection rates to preventing surgical site infections, such tools can provide a foundation for stronger infection control efforts. For the medical tourism industry, crisis could turn into opportunity. Will they and others rise to the challenge?

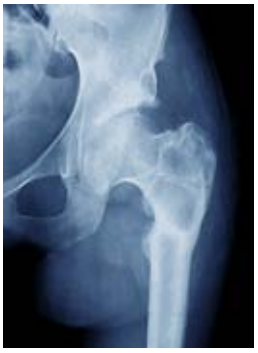
Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare: (1) No financial support for the submitted work from anyone other than their employer; (2) No financial relationships with commercial entities that might have an interest in the submitted work; (3) No spouses, partners, or children with relationships with commercial entities who might have an interest in the submitted work. (4) AS directs the strategic policy unit of Action on Antibiotic Resistance (ReAct) and was chair of the WHO/World Alliance for Patient Safety working group on antimicrobial R&D. AH is the executive director of ReAct and served as a member of the WHO/World Alliance for Patient Safety working group on rational use of antimicrobials. AH also works part time for the Swedish Strategic Programme against Antibiotic Resistance (Strama)/Swedish Institute for Infectious Disease Control.

Provenance and peer review: Commissioned, not externally peer reviewed.

1 Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *Lancet Infect Dis* 2010;10:597-602.
2 Dhar A. Task force to draft policy on antibiotics. The Hindu. 2010. http://hindu.com/2010/09/04/stories/2010090464081400.htm.
3 Tängdén T, Cars O, Melhus A, Löwdin E. Foreign travel is a major risk factor for colonization with Escherichia coli producing CTX-M-type extended-spectrum beta-lactamases: a prospective study with Swedish volunteers. *Antimicrob Agents Chemother* 2010;54:3564-8.
4 Vandenesch F, Naimi T, Enright MC, Lina G, Nimmo GR, Heffernan H, et al. Community-acquired methicillin-resistant Staphylococcus aureus carrying Panton-Valentine leukocidin genes: worldwide emergence. *Emerg Infect Dis* 2003;9:978-84.
5 European Antibiotic Resistance Surveillance System. EARSS Annual Report. 2008. www.rivm.nl/earss/Images/EARSS%202008_final_tcm61-65020.pdf.
6 Smith DL, Dushoff J, Perencevich EN, Harris AD, Levin SA. Persistent colonization and the spread of antibiotic resistance in nosocomial pathogens: Resistance is a regional problem. *Proc Natl Acad Sci USA* 2004;101:3709-14.
7 Deloitte medical tourism: consumers in search of value. Deloitte Center for Health Solutions. 2008. www.deloitte.com/assets/Dcom-UnitedStates/Local%20Assets/Documents/us_chs_MedicalTourismStudy(3).pdf.
8 Horowitz MD, Rosensweig JA, Jones CA. Medical tourism: globalization of the healthcare marketplace. *MedGenMed* 2007;9:33-42.
9 World Health Organisation. WHO urges countries to take measures to combat antimicrobial resistance. News release. 2010. www.who.int/mediacentre/news/releases/2010/amr_20100820/en/index.html.
10 Action on Antibiotic Resistance (ReAct). 2010. www.reactgroup.org.
11 Ferris TG, Torchiana DF. Public release of clinical outcomes data—online CABG report cards. *N Engl J Med* 2010; published online September 7.
12 Haynes AB, Weiser TG, Berry WR, Lipsitz SR, Breizat AH, Dellinger EP, et al. A surgical safety checklist to reduce morbidity and mortality in a global population. *N Engl J Med* 2009;360:491-9.

Hip resurfacing

Despite safety warnings, it remains an effective option in certain subgroups



SOVEREIGN ISM/SPL

James M Simpson fellow in hip surgery
jm.simpson@rcsed.ac.uk
Richard N Villar consultant orthopaedic surgeon, Richard Villar Practice, Spire Cambridge Lea Hospital, Cambridge CB4 9EL

Competing interests: None declared
Provenance and peer review: Not commissioned; externally peer reviewed.

Cite this as: *BMJ* 2010;341:c3459
doi: 10.1136/bmj.c3459

Metal on metal hip resurfacing is a type of hip replacement or arthroplasty where the head of the femur is preserved and shaped to receive a metal cap or resurfacing. This is distinct from a total hip replacement where the femoral head is excised and the prosthesis sits in the femoral shaft.

Recent results for hip resurfacing in several national joint registries[1 2] and the orthopaedic literature[3 4] have raised concerns. On 22 April 2010 the Medicines and Healthcare products Regulatory Agency (MHRA) issued a device alert for all metal on metal hip replacements, most of which will be hip resurfacings.[5] This, together with reports in the lay press, have raised concerns among patients and healthcare professionals.[6 7]

Total hip replacement, as distinct from hip resurfacing, is one of the most successful surgical procedures in terms of quality adjusted life years, second only to smoking cessation in terms of cost-benefit analysis using these measures.

Despite this, about one in 10 patients is dissatisfied with their outcome. The worst results in terms of implant survival have been seen in young, physically active men.[8] The 2004 Swedish arthroplasty register reported that a 73.5% implant survival rate at 13 years in 3122 men under 50 years of age compared with 95.7% in 30 809 women older than 75.[9] With current technology, younger patients are therefore destined to need multiple hip replacements in their lifetime. Functional outcome deteriorates after multiple revisions in these people. Consequently, surgeons try to avoid total hip replacement in younger patients. Hip resurfacing can delay this process by adding an additional step before total hip replacement.

The national joint registry for England and Wales reported a three year revision rate for all hip resurfacings of 4.5% (95% confidence interval 4% to 5%; n=11 770) compared with 1.3% (1.2% to 1.4%; n=86 524) for total hip replacement with a cemented femoral stem.[1] However, in men under 55 the three year revision rates were similar for hip resurfacing (3.7%, 3.0% to 4.7%; n=3131), uncemented total hip replacement (3.3%, 2.6% to 4.2%; n=3407), and cemented total hip replacement (2.5%, 1.7% to 3.7%; n=1364). Overall, the variation in performance between the different resurfacing designs was far more striking. The best, in terms of survival, was the Birmingham Hip Resurfacing manufactured by Smith and Nephew, Memphis, TN, USA (3.3%, 2.9% to 3.9%; n=6746) and the worst was the Articular Surface Replacement manufactured by Depuy, Warsaw, IN, USA (7.5%, 5.9% to 9.5%; n=1332).[1] This last design is no longer marketed in the United Kingdom.

In the Australian national joint replacement registry the overall eight year revision rate for total hip replacement was 4.9% (4.7% to 5.2%; n=147 422), and for hip resurfacing it was 6.1% (5.3% to 6.9%; n=12 093).[2] In men under 55 years

with osteoarthritis, and in the absence of infection, the seven year revision rates were similar for these procedures. Women have significantly poorer results for hip resurfacing and this is because they tend to have smaller components implanted. Smaller components (femoral head diameter ≤44 mm) had a four times greater risk of revision at seven years than larger components (femoral head diameter ≥55 mm).[2] The biomechanical basis for this difference is unclear.

Preoperative planning using radiographs should allow surgeons to identify who would be likely to receive smaller components so that alternative types of hip replacement can be considered. Alterations to the selection criteria for hip resurfacing have been successful in the past. An increased risk of femoral neck fracture was seen in perimenopausal and postmenopausal women as a result of hormone related bone density changes. Excluding these patients successfully reduced this complication.[10]

Perhaps the most worrying complication of metal on metal hip replacements is the development of pseudotumours. They seem to be related to excessive wear states in these metal on metal hip joints and subsequent metal ion hypersensitivity reactions, which can in extreme cases severely damage the tissues around these artificial joints.[3 4] The concerns over this complication largely prompted the MHRA device alert. Although it is potentially disastrous, this complication is thankfully rare, affecting about one in 1000 metal on metal hip replacements. The risk of an implant becoming infected after any type of joint replacement is also troubling and has formed part of the informed consent for these operations for many years. The risk of infection after joint replacement is 10-20 times that of developing a pseudotumour. Polyethylene wear debris produced by traditional total hip replacements also results in an inflammatory reaction that is behind most cases of eventual failure of these implants, although this occurs over a longer time period.

Hip resurfacing is a technically demanding procedure, and metal on metal implants do not tolerate poor positioning.[11 12] Certain designs are much more sensitive to poor positioning than others, and this is likely to be related to design differences. The basic science behind our understanding of how large head metal on metal joint replacements work is incomplete, and more work is needed on how they function in the human body rather than in the laboratory. Retrospective studies assessing the risk of cancer after metal on metal joint replacements from the late 1960s and early 1970s have been reassuring.[13]

Direct comparison between hip resurfacing and total hip replacement might not be justified. The two designs differ considerably and they might have different indications. The threshold for revision of hip resurfacing, particularly in the current climate, may also be lower than that for revision of a total hip replacement. The number of hip resurfacing procedures being performed has reduced dramatically as surgeons and patients become alarmed by the headline figures. Yet a closer look at the data shows that the operation is effective in young men in whom the orthopaedic community has been struggling to find reliable longer term treatment strategies. The combination of hip resurfacing followed by total hip replacement when the resurfacing fails remains an attractive and rational option.

1 National Joint Registry for England and Wales. Sixth annual report 2009. 2009. www.njrcentre.org.uk/njrcentre/AbouttheNJR/Publicationsandreports/Annualreports/tabid/86/Default.aspx.
2 Australian Orthopaedic Association National Joint Replacement Registry. Annual report. 2009. www.dmac.adelaide.edu.au/aoanjrr/publications.jsp?section=reports2009www.surfacehippy.info/aoanationalreg09.php.
3 Grammatopoulos G, Pandit H, Kwon YM, Gundle R, McLardy-Smith P, et al. Hip resurfacings revised for inflammatory pseudotumour have a poor outcome. *J Bone Joint Surg [Br]* 2009;91-B:1019-24.
4 Glyn-Jones S, Pandit H, Kwon YM, Doll H, Gill HS, Murray DW. Risk factors for inflammatory pseudotumour formation following hip resurfacing. *J Bone Joint Surg [Br]* 2009;91-B:1566-74.
5 Healthcare products Regulatory Agency. Medical device alert. All metal-on-metal (MoM) hip replacements (MDA/2010/33). www.mhra.gov.uk/Publications/Safetywarnings/MedicalDeviceAlerts/CON079157.
6 Porter M. Is hip resurfacing the best solution for arthritis? *Times* 2009. www.timesonline.co.uk/tol/life_and_style/health/expert_advice/article6925165.ece.
7 Ungoed-Thomas J, Duffill G. Tumour fear over metal hip replacements. *Times* 2010. www.timesplus.co.uk/sto/?login=false&url=http://www.thesundaytimes.co.uk/sto/news/uk_news/Health/article265825.ece.
8 Northmore-Ball MD. Young adults with arthritic hips. Should be offered alternatives to total hip replacement. *BMJ* 2007;315:265-6.
9 Herberts P, Karrholm J, Garellick G. Swedish hip arthroplasty register annual report 2004. Swedish Hip Arthroplasty Register, 2005.
10 Mont MA, Seyler TM, Ulrich SD, Beaule PE, Boyd HS, Grecula MJ, et al. Effect of changing indications and techniques on total hip resurfacing. *Clin Orthop Relat Res* 2007;465:63-70.
11 Angadji A, Royle M, Collins SN, Shelton JC. Influence of cup orientation on the wear performance of metal-on-metal hip replacements. *Proc Inst Mech Eng H* 2009;223:449-57.
12 McGrory B, Barrack R, Lachiewicz PF, Schmalzried TP, Yates AJ Jr, Watters WC III, et al. Modern metal-on-metal hip resurfacing. *J Am Acad Orthop Surg* 2010;18:306-14.
13 Visuri T, Pukkala E, Paavolainen P, Pulkkinen P, Riska EB. Cancer risk after metal on metal and polyethylene on metal total hip arthroplasty. *Clin Orthop Relat Res* 1996;329:S280-9.

Oil, health, and health care

Future health and prosperity require that we prepare for life without cheap oil

Angela E Raffle consultant in public health, NHS Bristol, Bristol BS1 3NX
angela.raffle@bristol.nhs.uk

Cite this as: *BMJ* 2010;341:c4596
doi: 10.1136/bmj.c4596

The April 2010 oil leak in the Mexican Gulf illustrates the risks being taken to extract oil from inaccessible fields, and in June a Lloyd's 360° risk insight report said, "We have entered a period of deep uncertainty in how we will source energy for power, heat and mobility and how much we will pay for it."[1] The reason why such damaging extraction methods are pursued, and why Lloyd's are telling us we face a "new energy paradigm" rather than normal market volatility, is that oil discoveries peaked 40 years ago, and oil supply is probably at its maximum, with decline soon to follow.[2] This has substantial implications for transport, food, jobs, health, and health care.[3] Yet many people still haven't heard of "peak oil" and few are discussing it.

The International Energy Agency says that we are running out of time to build the skills, systems, and infrastructure needed for a prosperous future.[4] They forecast a depleted energy supply in the next decade. Energy availability underpins economic growth, and without the opportunity for future repayment of debt the financial system as we know it could stop working.[5]

The science of peak oil is not difficult.[6] Nation by nation, oil discovery has risen then declined in a bell shaped curve.


PHILLIP HAYSON/SPL

Production follows a similar curve and peaks some 40 years after peak discovery. Global discovery peaked in the 1960s. Exponential growth in world population, debt, environmental damage, and rate of depletion of natural resources all link back to this energy rich, highly versatile, and easily transportable fuel.[5] There is nothing equivalent to replace it.

Until 2005, the United Kingdom was a net exporter of North Sea oil and gas. Now the UK relies increasingly on imports. Government forecasts for fuel supply include a major portion yet to be determined.[7] On March 22 the Department for Energy and Climate Change held a seminar, under Chatham House rules, examining "potential future oil supply constraints." Jeremy Leggett of the UK industry peak oil taskforce, commenting to the *Guardian*,[8] said "Government has gone from the BP position—'40 years' supply left, the price mechanism works, no need to worry'—to 'crikey.'" It is too early to say how this might be reflected in the new coalition government's policies.

Some cities in the UK are aware of peak oil implications. For example, leaders in Bristol commissioned a report in 2009 on the implications of peak oil.[3] This has helped stimulate work to develop a Bristol Energy Company and a local currency, to analyse the vulnerabilities of the current food supply system, and to adopt a "climate change and energy security framework." Incorporating peak oil preparedness into England's official local government planning mechanisms—local transport plans and local development frameworks—is an uphill struggle because central government policies still favour the needs of big food corporations, construction industries, and the road lobby above the need for resilient local systems.

The healthcare conclusions in Bristol's peak oil report are that oil is a primary raw material for many drugs, equipment, and supplies; that transport for patients, staff, deliveries, and services is heavily oil dependent; that currently suppliers are not required to provide business continuity plans around fuel supply shortages; and that rising oil costs would seriously affect health service budgets.[3] On the positive side, the report noted the resilience afforded by the following facts: most people live within a mile of their nearest general practice; the NHS is used to responding to emergencies and making rapid changes; walking, cycling, and locally grown food are good for health; and the NHS Carbon Reduction Strategy for England does acknowledge peak oil.[9] What this means is that health care will change, whether we like it or not, and that carbon reduction, fuel depletion, and financial stringencies have to be looked at together.

Experts on peak oil and health experts have examined this challenge together at three workshops, and some common themes emerge. These concern the need for simpler more robust systems that are capable of local maintenance, and the importance of fairness regarding access to food, water, transport, and essential health care. The box summarises possible features identified as characteristic of a healthy prosperous society in the future. Because the workshops explored success not failure the goals may appear idealistic. The alternative could be very different.

Until recently, peak oil was mainly seen as a crackpot theory promulgated by doom merchants who hate progress. This probably reflects the influence that corporate publicity strategies and pressure to preserve confidence in global markets have on the mainstream media.[10] The Bristol peak oil report and Chris Martenson's *Crash Course* are the first steps towards changing this attitude.[3 5]

Summary outcomes from three future forecasting workshops examining effects of peak oil on health and health care

Features of a society that has successfully reduced its reliance on fossil fuel:

Healthcare facilities, equipment, supplies

All essential drugs are now produced without petrochemicals, some locally
Energy intensive and high cost methods of diagnosing and treating illness are a thing of the past
The most essential and best value aspects of modern health care have been preserved; those of only marginal benefit have been abandoned
All NHS estate is a net energy generator
Every NHS facility is accessible on foot, by bicycle, and by public transport
Digital infrastructure is used for high priority communication, including that between patients and health services
Landline telephone and radio are important

Health and recreation

Health and physical resilience are highly valued, and it is regarded as normal to safeguard health through the way that we live and work
Physical activity is for most people a non-negotiable part of everyday life, food is plainer but healthier, and local breweries are numerous
Local drama, art, music, dance, and celebration are commonplace

Land and the built environment

Towns and cities have high density housing—more lodgers, more boarding houses, and more shared housing
All land and space that can be is used for food production. Many more people are employed in food growing and preparation, and people's involvement with food is far greater
More people live and work in agricultural areas
Buildings are multi-use and adaptable
Many people work from home, or from shared "work cafes"

People

Communities have a network of registered volunteer carers and emergency helpers
Everyone participates in training within the local community
Everyone does some form of volunteering work for their local community
Health professionals work closely with informal carers
Every community has an emergency plan
Health care is seen as a community resource with priority given to those with greatest needs

Rules

There are local exchange trading schemes and local currencies
Legal structures are different, limited liability is gone, drivers of growth are gone, and the ability of an individual to pursue expensive legal challenges is gone
The norm is for systems designed for the prosperity of the community and the preservation of non-renewable resources
Health care is rationed and some conditions cannot be treated

1 Froggatt A, Lahn G. Sustainable energy security; strategic risks and opportunities for business. Lloyds 360 risk insight. 2010 www.lloyds.com/News-and-Insight/360-Risk-Insight/Research-and-Reports/Energy-Security/Energy-Security.
2 Oil Depletion Analysis Centre. Preparing for peak oil: local authorities and the energy crisis. 2009. www.odac-info.org/sites/odac.postcarbon.org/files/Preparing_for_Peak_Oil.pdf.
3 Osborn S. Building a positive future for Bristol after peak oil. 2009. www.bristol.gov.uk/ccm/content/Environment-Planning/sustainability/file-storage-items/peak-oil-report.en.
4 International Energy Agency. World energy outlook. 2008. www.worldenergyoutlook.org/docs/weo2008/WEO2008_es_english.pdf.
5 Martenson C. The crash course. www.chrismartenson.com/crashcourse.
6 UK Industry Peak Oil Taskforce. The oil crunch; securing the UK's energy future. 2010. http://peakoiltaskforce.net.
7 Department of Energy and Climate Change. The UK low carbon transition plan—national strategy for climate change and energy. 2009. http://centralcontent.fco.gov.uk/central-content/campaigns/act-on-copenhagen/resources/en/pdf/DECC-Low-Carbon-Transition-Plan.
8 Energy minister will hold summit to calm rising fears over peak oil. *Guardian* 2010. www.guardian.co.uk/business/2010/mar/21/peak-oil-summit.
9 NHS Sustainable Development Unit. Saving carbon improving health; NHS carbon reduction strategy. 2009. www.sdu.nhs.uk/page.php?area_id=2.
10 Bunting M. Too fearful to publicise peak oil reality. *Guardian* 2009. www.guardian.co.uk/commentisfree/cif-green/2009/nov/10/peak-oil-fear-economic-establishment.