The benefits of recession

Health professionals around the world are rightly asking difficult questions of their governments as cuts to health services are implemented within national austerity packages. The global financial recession has led to an international health recession, with the exception of a small number of high-growth economies, such as China. The fear that governments will use their economic predicaments to cut back state funding for health is not imaginary. The UK is a prime example of a country in which politicians have exploited an emergency to open up new markets for any willing private provider. But while all doctors must continue to be vigilant of their governments, a recession does have at least one advantage. It invites us to be sure that the money we do spend on health is spent wisely.

Questions of accountability are now political as well as professional priorities. The movement towards comparative effectiveness research in the USA is one example. We must surely determine, the argument goes, whether one approach to a particular health problem is superior to another. Is treatment A better than treatment B for a given disease? We must be accountable for the results we expect and resources we invest in health. It is difficult to see the controversy behind such a proposition. But the USA is also a good, if extreme, example of how questions of accountability become distorted through the lens of politics. One of the drawbacks of democracy—perhaps one of the flaws of human rationality—is that common sense often dies on the altar of partisan political expediency. And so the notion of comparative effectiveness, and thereby the denial of absolute clinical freedom to practise any kind of evidence-free medicine one likes, is transmuted into the creation of "death panels".

Internationally, accountability is perhaps an even more urgent priority. Voters are mostly happy to give part of their taxes to human development programmes in low-income and middle-income countries. When polled, they see it as a moral duty to take some kind of responsibility for the world's disadvantaged peoples. That spirit of humanitarianism is expressed most acutely at times of natural disaster—a famine, an earthquake, a flood. But there is a deep-seated desire in most of us—a desire that can be proven scientifically (it is called game theory)—to find a fair balance in the distribution of global resources. Equity is encoded into human DNA. We might never find a specific gene for our desire for fairness, but we should recognise (and joyfully celebrate) the fact that our idea of justice is deeply rooted in human psychology and culture.

But even we humans have our limits. Our willingness to pay for poverty in Africa, for example, extends only as far as we can be sure that the money being spent is not going into the private bank accounts of despotic rulers or corrupt officials. The public begins to withdraw its support for international health aid when their own standards of living are seriously threatened and when it seems that the money they are giving is being misused. Sadly, corruption is rife in the field of global health. One rule of thumb we hear is that any donor should expect 30% of their aid to be siphoned off—one might say stolen—for personal gain in the recipient country. When times are good, difficult questions about where aid money goes can be conveniently silenced. But during today's times, these issues have to be confronted. The ongoing UN Commission on Information and Accountability for Women's and Children's Health is an example of a high-level political mechanism to protect the future of international aid for a long-neglected sector in global health. The results of this Commission, to be delivered to the World Health Assembly in May, aim to define the meaning of accountability for results and resources in maternal and child health programmes. The conclusions of the Commission will have great relevance for all global health initiatives.

Underlying all questions of accountability is the issue of measurement. There can be no accountability in health without metrics. Whether we are talking about the efficacy of a new medicine for one type of cancer in the USA or the effectiveness of a programme to distribute insecticide-treated bednets to families in Kenya, trends in child mortality across India or conditional-cash transfer policies in Mexico, metrics are the foundation for our judgment. It is perhaps surprising, even shocking, that only now is the first global health metrics and evaluation conference to be held in Seattle on March 14–16 this year. The meeting offers the first opportunity to embed the science of measurement into global health thinking and policy making. It is a landmark event. It is also a sign of our troubled times. We hope that it is not a one-off gathering. Accountability through measurement is the route to a fairer society. We all have a stake in that future.

■ *The Lancet*

Tim Ireland/PA

See **Special Report** page 797

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Adolescent girls: taking centre stage

Giacomo Pirozzi/Panos

For more on the **UN Adolescent Girls Task Force** see http://www.unfpa.org/public/cache/offonce/news/pid/4969

For more on the **55th Session of the Commission on the Status of Women** see http://www.un.org/womenwatch/daw/csw/55sess.htm

The aspiration is ambitious: to improve the lives of adolescent girls with a comprehensive package of interventions tailored to their needs. In advance of International Women's Day on March 8, the UN Adolescent Girls Task Force (UNAGTF), a global initiative designed to draw on the expertise of seven contributing UN agencies, briefed governments and civil society organisations as part of the 55th Session of the Commission on the Status of Women. UNAGTF is in its infancy—it was formed in March, 2010, in recognition of insufficient investment in adolescent girls, and aims to accelerate progress towards the Millennium Development Goals in 2015.

In developing countries, which are home to 500 million adolescent girls, adolescence is a period fraught not only with mental and physical transitions, but also with issues that prematurely catapult young people into adulthood. They face poverty, child or forced marriage, pregnancy at a young age, risk of HIV infection, and violence, often without the benefit of an education. "Adolescence is a tumultuous time, especially for the youngest, poorest, most marginalized girls", says Babatune Osotimehin, the recently appointed Executive Director of the UN Population Fund, and the most vulnerable girls are invisible in many existing development programmes.

UNAGTF believes that the age-group of 10–14 years is the key to prevention of rights violations. This window is crucial to educate and improve the health of girls, and to target the gender gap by shaping the attitudes of boys. Programmes are already underway in Malawi, Liberia, Ethiopia, and Guatemala. UNAGTF's holistic approach to programmes is designed to empower girls to speak up, become leaders, and participate in policy making. "Respecting, protecting and fulfilling the rights of adolescent girls has a positive catalytic effect on societies as a whole and contributes to the achievement of gender equality and poverty alleviation." This International Women's Day, we recognise that investment in today's population of adolescent girls will hugely benefit the lives of future generations. The challenges are formidable, but the potential for change is great. ■ *The Lancet*

Taking shared decision making more seriously

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For the **Dartmouth Atlas report** see http://www.dartmouthatlas.org/downloads/reports/Decision_making_report_022411.pdf

Clinicians are used to being the drivers of decision making in medicine. They hold the relevant knowledge, apply it to their patients, and make recommendations that are, more usually than not, taken up. But while this approach might be acceptable for many conditions for which there is a best choice for care, when it comes to illnesses for which several equally valid treatment options exist, patients' preferences should prevail. Yet a new US study shows that this is rarely the case, and clinicians' opinions and personal beliefs often dominate decision making.

The Dartmouth Atlas Project found that whether patients underwent elective surgery largely depended on where they lived and the clinicians which they saw. For example, patients with heart disease in Elyria, Ohio, were ten times more likely to have a procedure such as angioplasty or stents than were those in Honolulu. And women older than 65 years living in Victoria, Texas, were seven times more likely to undergo mastectomy for early-stage breast cancer than were women in Muncie, Indiana. Such wide variations underscore the need for improving shared decision making, say the authors.

The importance of shared decision making is clear, especially when considering a disease such as early-stage breast cancer, in which mastectomy or lumpectomy and radiotherapy have similar survival outcomes but are very different treatments for a patient to undergo. It is crucial that doctors inform patients of the pros and cons of each and invite them to participate in the management choice.

Efforts to aid the doctor–patient dialogue are being made, mainly in the USA. The US Affordable Care Act has provisions to fund the development of shared decision making. And the Dartmouth-Hitchcock Medical Center in New Hampshire already has the nation's first dedicated Center for Shared Decision Making, where counsellors help patients to become informed about treatments.

Although there is much still to learn about the art and science of shared decision making, progressive measures to empower patients with knowledge about treatment options should be welcomed by doctors. Only then will medicine begin to move away from a clinician-centric model of care to one in which patients can truly participate in decision making. ■ *The Lancet*

Unravelling the role of denosumab in prostate cancer

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Advances in cancer therapies have brought about changes in the treatment of metastatic prostate cancer. Because prostate cancer usually metastasises to the bone,[1] strategies to target the bone are being actively developed (panel). Zoledronic acid was the first approved agent for retarding skeletal events in men with metastatic prostate cancer, on the basis of the phase 3 trial[2] showing that it was superior to placebo. Since then, this drug has become a standard adjunctive treatment for men with prostate cancer with bone metastases.

In *The Lancet*, Karim Fizazi and colleagues[3] present a randomised phase 3 trial of denosumab versus zoledronic acid to treat bone metastases in just over 1900 men with castration-resistant prostate cancer. Denosumab is a human monoclonal antibody against the receptor activator of nuclear factor κ-B ligand (RANKL), which is responsible for osteoclast formation, differentiation, and survival.[4] The primary endpoint of the study was time to first on-study skeletal-related event, defined as either the occurrence of a pathological fracture, bone radiation or surgery, or spinal cord compression. Denosumab was better than zoledronic acid in delaying that endpoint by 18%, with a difference in the median time of 3·6 months. Exploratory endpoints of overall survival, investigator-assessed progression, and progression of prostate-specific antigen concentration were similar between groups. Serious adverse events were also much the same between denosumab and zoledronic acid, apart from raised rates of hypocalcaemia (13%) and osteonecrosis of the jaw (2%) in the denosumab group.

Apart from meeting the primary endpoint, the logistical advantages of the use of denosumab over zoledronic acid are clear. Denosumab is easier to give (subcutaneous) than is zoledronic acid, allowing for shorter visit times and applicability in various physicians' office settings by removing the need for an infusion clinic. Furthermore, denosumab reduces the need for management of acute phase reactions and renal monitoring or dose adjustments, although caution should be exercised with patients who have poor baseline kidney function. Additionally, the on-study use of docetaxel in about a third of patients[3] suggests it is safe to give denosumab to patients who are actively undergoing chemotherapy.

Although the results of this trial herald yet another important milestone in the treatment of men with metastatic castration-resistant prostate cancer, several issues come to mind. First, in this era of changing health-care policies, cost-effectiveness remains a contentious issue. When zoledronic acid was first introduced, many questions were asked about routine introduction of this treatment in all patients with metastatic prostate cancer. In a cost-effectiveness analysis of zoledronic acid compared with placebo,[5] the nominal cost per skeletal complication avoided was about US$12 300, and thus the argument was that treatment with this drug was worthwhile. Although drug costs are variable and generally country-dependent, similar cost-effectiveness trials between zoledronic acid and denosumab have yet to be done.

Second, with the emergence of newly approved agents for metastatic prostate cancer, the appropriate sequencing of these agents is now a burgeoning question (such as timing of immunotherapy, institution of cytotoxic chemotherapy, or application of novel hormonal agents). The same challenges could emerge with the use of bone-targeting agents. Because the use of denosumab encompasses the same population of patients for whom zoledronic acid would have been prescribed, should zoledronic acid be totally replaced by denosumab? Is there a population that would benefit from one agent over another? Is the difference in the median time to first skeletal-related event of 3·6 months

***Panel:* Therapeutic strategies targeting bone signalling and metastases in prostate cancer**

Targeting bone-forming osteoblasts

- Bone-seeking radiopharmaceuticals (samarium-153, strontium-89)
- Inhibition of endothelin axis (ZD4054)
- Targeting insulin-like growth factor (IGF) axis
- Targeting transforming growth factor (TGF) axis, Wnt signalling, and bone morphogenic proteins (BMP) pathways

Targeting bone-resorptive osteoclasts

- Bisphosphonates (zoledronic acid)
- Inhibition of receptor activator of nuclear factor κ-B ligand (RANKL; denosumab)
- Inhibition of osteoclast function (cathepsins, Src homology 2 inhibitors, interleukin-6 inhibitors)

clinically significant enough to justify the choice of denosumab over zoledronic acid, in view of the potential increased cost and especially in the absence of survival or progression benefit? Although there are data on the feasibility of giving denosumab after zoledronic acid,[6] long-term data on the effect of denosumab in patients who have previously been given zoledronic acid remains to be defined.

Third, although the adverse event profiles are fairly similar for both agents, one notable side-effect is the development of osteonecrosis of the jaw. A potentially debilitating disorder, osteonecrosis of the jaw was increasingly identified after 2003, in association with bisphosphonate use.[7] In Fizazi and colleagues' study, this side-effect occurred (albeit without a significant difference between treatment groups in the short follow-up) in 22 patients (2%) in the denosumab group compared with 12 patients (1%) in the zoledronic acid group. Although several hypotheses and risk factors have been identified in the development of this disorder, the exact mechanism by which osteonecrosis of the jaw develops is not entirely understood even for bisphosphonate use,[8] much less so with denosumab. Therefore close monitoring is warranted. Fourth, denosumab had better efficacy for the primary endpoint than did zoledronic acid, but further quality-of-life and pain-response data would be important aspects to report on, especially because the most common side-effects of fatigue, bone pain, and asthenia, among others, were reported almost equally in both groups.

Despite our questions about the use of denosumab, this drug remains a welcome addition to the options available for the treatment of metastatic prostate cancer. As with other agents that have been successful in the metastatic setting, moving this drug towards early stages of disease is the logical next step in the identification of its other potential uses. Denosumab has already been shown to reduce skeletal fractures in men who are undergoing androgen-deprivation therapy without overt clinical metastasis.[9] Clinical trials assessing the use of denosumab in the delay of onset of metastasis have been promising and will help further define its role in prostate cancer.[10]

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I have received honoraria for serving on a speaker's bureau for Sanofi-Aventis and participating in an advisory board from Centocor Ortho Biotech.

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Chronic fatigue syndrome: where to PACE from here?

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In *The Lancet*, Peter White and colleagues[1] report the four-group PACE randomised trial in adults with chronic fatigue syndrome. PACE stands for "Pacing, Activity, and Cognitive behaviour therapy: a randomised Evaluation". The investigators report the efficacy of three behavioural interventions and specialist medical care. The Article provides a useful panel to summarise the interventions.

PACE tested the safety of the interventions. Concerns about the safety of cognitive behavioural and graded exercise therapy have been raised more than once by patients' advocacy groups. Few patients receiving

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