

## Safety and Risk in Practice

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### Drug research: What does it really cost?

The fact that good drugs are financially out of reach of much of the world's population is unquestioned; the World Health Organization has documented the issue for many years, and progress towards resolving it is slow. Even in the industrialized world, the cost of medicines is proving a major burden to health services, which one after another have sought ways to circumvent the problem. The massive inflow of low-cost drugs from Canada into the USA's public health services is only one example; it is however a striking one when one bears in mind that the United States, more than any other country, has vehemently defended the level of earnings enjoyed by its pharmaceutical industry, supposedly necessary if a flow of new, better and safer drugs is to be guaranteed.

So what does it really cost to create and develop a new drug that will benefit humanity? For a long time, policy makers have allowed themselves to be persuaded by figures disseminated by industry itself, most of which originated with the so-called Tufts Centre for the Study of Drug Development. Over the course of two decades, that Centre's estimates have risen dramatically; in 2003, DiMasi and his colleagues published a figure of 802 million dollars [1], some fifteenfold higher than when the Centre first began drawing up such figures a quarter of a century ago in 1979. There are plenty of reasons why such figures have in recent years been looked at more and more critically. One is already touched on, the reluctance of the public services to continue bearing the present level of drug expenditure, leading them to look carefully at the economic justification for high prices, if such justification there be. Another reason lies in the work of Laing [2] and others [3], who have used publicly available data, particularly from the U.S. Securities and Exchange Commission, to show that the amounts actually spent on research by major American firms pale into insignificance before the amounts going to promotion, administrative expenses and profit. In addition, there is increasing questioning of the way research money is being spent, much of it today delivering products of only marginal health importance and virtual copies of earlier drugs. Finally, with many of the safety studies for industry being carried out in public institutions, one has data available which show the real costs of this work; safety is not as unaffordable as Tufts seeks to suggest.

A recent critical analysis of the facts was published by *La Revue Prescrire* in Paris late in 2003 [4]. It concludes that the notion that vast expense is needed to develop a useful new drug is no more than a "grand illusion". The Tufts' figures are faulted on numerous grounds. The Centre, largely funded by the pharmaceutical industry itself, came in 1980 with an average R&D figure of \$54 million, which by 1991 had risen to \$231 million, and since then has escalated year by year. The estimates are based on data provided confidentially to the Centre by various American companies; it includes various incidental expenses, taxes and the cost of loaning, excludes the figures for those many drugs essentially discovered in universities, and includes types of spending which are commercial rather than scientific ("promotional research"); the duration of research is much overestimated and the tax benefits obtained by undertaking innovation are largely ignored. Above all, figures from other and more readily verifiable sources strongly suggest that the true average cost of new drug discovery and development is very much lower.

These things matter, and work like this, undertaken by impartial bodies, needs to continue. The pharmaceutical industry owes a duty to the public to provide not only better and safer drugs but also a true

account of the way it uses the vast sums of money entrusted to it by nations to supply products. There is now a lot of reason to believe that much of this money is not being spent to the public benefit.

## References

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- [3] Anon, Profiting from pain – Where prescription drug dollars go, *Families USA*, 2002, 37 pp.
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## A mother's death a minute

Our distinguished London contemporary *The Health Summary* calls our attention to a new report from WHO, UNICEF and UNFPA showing that a woman living in sub-Saharan Africa has a 1 in 16 chance of dying in pregnancy or childbirth. This compares with a 1 in 2,800 risk for a woman from a developed region.<sup>1</sup>

Of the estimated 529,000 maternal deaths in 2000, 95% occurred in Africa and Asia, while only 4% (22,000) occurred in Latin America and the Caribbean, and less than 1% (2,500) in the more developed regions of the world. Experience from successful maternal health programmes shows that much of this death and suffering could be avoided if all women had the assistance of a skilled health worker during pregnancy and delivery, and access to emergency medical care when complications arise.

“Many women deliver their children alone or with family members or other untrained attendants who lack the skills to deal with complications during delivery” said Dr Lee Jong-Wook, Director-General of the World Health Organization. “Skilled attendants are vital because they can recognize and prevent medical crises and provide or refer for life-saving care when complications arise. They also provide mothers with basic information about care for themselves and their children before and after giving birth”.

Reducing maternal mortality is a key factor in ensuring that all children, especially in the world's poorest countries, survive and thrive through adolescence. “These new estimates indicate an unacceptably high number of women dying in childbirth and an urgent need for increased access to emergency obstetric care, especially in sub-Saharan Africa”, said UNICEF Executive Director Carol Bellamy. “The widespread provision of emergency obstetric care is essential if we want to reduce maternal deaths”.

The maternal mortality ratio, which measures the number of deaths to women per 100,000 live births due to pregnancy-related complications, was estimated to be 400 per 100,000 live births globally in 2000. By region it was:

Africa	830
Asia (excluding Japan)	330
Oceania (excluding Australia and New Zealand)	240
Latin America and the Caribbean	190
Developed countries	20

<sup>1</sup>[www.who.int/reproductivehealth/MNBH/maternal\\_mortality\\_2000/index.htm](http://www.who.int/reproductivehealth/MNBH/maternal_mortality_2000/index.htm).

Worldwide, 13 developing countries accounted for 70% of all maternal deaths. The highest number occurred in India where 136,000 women died, followed by Nigeria, where there were 37,000 deaths.

In 2000, world leaders agreed to reduce maternal mortality by three-quarters by 2015 as part of the Millennium Development Goals. Tracking progress remains difficult, except where comprehensive registration of deaths, including causes of death, exists. For this reason, the use of indicators such as the proportion of women who have a skilled attendant at delivery is essential to track change. The use of skilled attendants at delivery in developing countries increased between 1990 and 2000 from 42 to 52%, suggesting a potential decrease in maternal deaths. Findings show the greatest improvements in South-East Asia and Northern Africa and the slowest change in sub-Saharan Africa, which went from 40% in 1990 to 43% in 2000.

Most maternal deaths and disability occur as the result of one or more of three delays:

- in recognising complications,
- in reaching a medical faculty, or
- in receiving good quality care.

Efforts to address these delays are essential in order to save the lives of mothers and babies. Education on family planning and the provision of family planning services of high quality can also make a difference. More lives could also be saved if women had access to voluntary family planning to ensure that births are spaced properly, as well as skilled attendance at delivery, and emergency obstetric care.

The death of a mother during pregnancy or childbirth, as *The Health Services* puts it, is a human tragedy for the individual, the family and society. The chances of survival, not only of the newborn but also of the other children, are substantially diminished when the mother dies.

### **Routine pre-natal genetic testing – a benefit with complications**

In a number of western countries, with the United States in the lead, it has become almost a routine in pre-natal care to undertake a series of genetic tests on the foetus; if not a universal routine it is at least a practice which is followed when even the slightest of reasons for it seems to be present. Prenatal genetic testing has its merits; Prof. Sonia Mateu Suter of George Washington University's Law School, who is both a law teacher and a qualified medical geneticist, is now prominent among those who in recent years have pointed to some of its social and psychological risks and called for its more prudent use [1].

The problem with any form of genetic testing is that it is based on a science which is still extremely young, and where the volume of existing knowledge is still heavily outweighed by the volume of our ignorance on some essential matters which it raises. The issue has long been discussed with respect to genetic testing of adults for their potential to develop particular diseases. As Prof. Suter puts it: "A woman might learn that she has the BRCA1 gene, but data are still uncertain about precisely what this means in terms of her risk of breast or ovarian cancer and what she can do to reduce this risk. People with a family history of Huntington Disease may choose to find out whether they have the gene that virtually guarantees they will develop the disease, if they live long enough. But it is currently impossible to predict the age of onset and no cure or prevention is available. As a result, anxiety and distress can be associated with finding out that one does or does *not* have a late-onset gene. Geneticists and ethicists have therefore urged caution and care in the decision-making process. More importantly, many have suggested that knowledge may not always benefit everyone. For some it can be "toxic".

The same considerations apply to genetic testing of the foetus, and indeed to other diagnostic routines used in pregnancy, such as ultrasound and even sex determination. It can be dangerous to be ignorant.

Yet it can also be dangerous to be handed information when one does not know what to make of it or what to do about it, and even the experts cannot give reliable advice. That fact, as Prof. Suter argues, has generally been overlooked by those resorting ever more frequently, and sometimes as a routine, to genetic testing in pregnancy. As Barbara Rothman put it when discussing amniocentesis in 1986 [2], prenatal testing has become part of social norms and expectations. So accepted a part of pregnancy is it now in the U.S. that women who decline such testing must be prepared with explanations and justifications. People ask “why not?” Nobody asks “why?” When Prof. Suter herself was pregnant at a relatively late age, she found that people talking to her about prenatal testing “did not ask *whether* I underwent amniocentesis or CVS, but instead *what kind of testing* I chose”. One explanation for this situation is that since the technology to perform such testing is available it is almost automatically offered and accepted; it is simply assumed that since it is a new development it is a good and necessary one. In fact, one could well argue that this is only the case for a limited group of pregnancies.

Several studies, notes Prof. Suter, have shown that one of the main reasons why patients seek prenatal testing is for reassurance. One intelligent woman in her early thirties came to the George Washington University clinic because she had been exposed to chemotherapy and radiation treatment for breast cancer a few years before her pregnancy.

“Although no data suggested that the prior treatment increased her risks above the 3–5% population risk of birth defects, we had to acknowledge that few studies had been conducted. We offered her an amniocentesis, primarily for reassurance, even though it was not technically medically indicated. We emphasized, however, that the test could only rule out chromosomal abnormalities and spinal defects, as well as any structural abnormalities that might be observed in an ultrasound. It could not, however, detect conditions that worried her, such as most forms of mental retardation, deafness and blindness. A few days later when she came in for the amniocentesis, as if she had forgotten the prior discussion, she asked if the test would rule out mental retardation, deafness and blindness. Even after hearing again about the limits of the test, she apparently could not absorb that information . . .”

A legal aspect of the problem in the US is the existence of “wrongful birth” as a cause of legal action; according to this doctrine, a genetic professional can potentially be held liable for birth defects in a patient’s child if he did not meet the standard of care in offering prenatal testing to a high risk patient, failed to diagnose a detectable defect through prenatal testing, or failed to inform the patient about a detected defect. In order to succeed in such a case, the woman will have to demonstrate that she would have terminated the pregnancy had she learnt of the defect in time. Whether the risk of such actions against genetic professionals is a real one or not, it is evident that even the theoretical possibility of such proceedings may be a motivating factor in carrying out pre-natal testing in many or all women. It certainly led the health professions to offer MAFP (maternal serum alpha-foetoprotein) screening to all pregnant women – a test method which can demonstrate an increased risk of neural tube defects. This course was followed despite the fact that this is merely a screening test, which can demonstrate a raised risk but does not itself show whether the defects in question actually exist or will occur.

Prof. Suter has made it clear that widespread *availability* of genetic testing is a good thing, but such testing must not become an obligation for either the professional or the patient, and in every case a woman should be informed in understandable terms what such tests can and cannot show, and it should be made entirely clear to her that there is no compulsion. The latter point is not well appreciated; one study in Finland [3] showed that half of the women interviewed believed that MAFP screening was compulsory; in California, where health professions must *offer* such screening to every pregnant women, more than a third of women interviewed believed that they were obliged to accept the offer [4].

Finally, it is surely vital for any woman in whose pregnancy a genetic tests shows a positive result to be carefully counselled. All too easily, a positive test can lead to severe distress, and to a decision – which the woman may well later regret – to terminate the pregnancy.

## References

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- [2] B.K. Rothman, *The tentative pregnancy: How amniocentesis changes experience of motherhood*, 1986.
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## Unhygienic hygiene?

Elsewhere in this *Journal*, an account is given of a recent Scandinavian scandal involving a less-than-hygienic mouth swab used in seriously ill patients. Such tales – and they reach the medical literature from time to time – do cause the observer to wonder how many other hygienic practices are rather less than optimal, persisting in their current form only because no-one can be troubled to change them.

Toilet paper – is there anyone who could seriously defend it? Any investigator dropping in from another planet to take a look at civilized society might well ask the question. Defaecation, once or more daily, is a physiological necessity which is decked over with as much secrecy and as much hygienic decorum as possible. The act is performed behind a closed and locked door, the surroundings are designed for easy cleansing and disinfection, the excreta are discreetly rinsed away into the sewers, and there is commonly provision for some form of deodorant treatment of the immediate environment. Yet having defaecated, the civilized human then proceeds to clean his anal region by rubbing porous paper across it, thereby infecting his hands and a substantial area of perianal skin. He may or may not wash his hands. He is unlikely to wash the perianal area, which is hastily covered with clothes, ready to be contaminated in their turn, and to contaminate others who handle them.

Developing countries, and particularly the south-east Asians, have for generations or centuries followed a more sensible approach – the bottle of water, ready to hand in the toilet, to wash the still moist infected material away and into the drain, leaving the skin clean. In its more advanced form, the technique involves a toilet in which a small spray, placed in the toilet itself or on a hand appliance, can be applied at the turn of a tap or by pressing a pedal. The apparatus is in production and on sale even in western countries, yet it has never really caught on. Will someone explain to this column why not?