B 5 **Medicine**

There are major problems with the way medicines are developed, marketed, priced, prescribed and consumed across the world. Three underlying factors deserve particular attention: a patent-driven system for pharmaceutical innovation; the predominance of profit-seeking actors within the sector; and the failure of public institutions to correct market failures and protect the public good.

These three factors were described in some detail in the first *Global Health Watch*. This chapter builds on that analysis by focusing on two policy issues:

- New mechanisms for financing and giving incentive for pharmaceutical research and development (R&D).
- The growing threat of antibiotic resistance.

The Innovation + Access (I+A) movement has brought the first issue to the discussions of the World Health Organization's Intergovernmental Working Group on Public Health, Innovation and Intellectual Property. An emerging coalition, Action on Antibiotic Resistance (ReAct), has begun to raise the profile of the second issue. The discussion of each flags serious challenges to improved innovation and affordable access to essential medicines. By no means though does this chapter discuss all the responsible factors. Other concerns which plague health-care systems include poor quality clinical care, ineffectual drug supply and distribution systems, and the lack of infrastructure required to ensure an effective cold chain.

A better system of pharmaceutical R&D

Problems with the current system

The public sector provides for extensive funding of research, training of the scientific workforce, and paying for the procurement of pharmaceuticals. Taking into account tax credits, the public sector provides 60 per cent of the funding for global health R&D (GFHR 2006). Yet the priorities of pharmaceutical R&D are largely shaped by the granting of patents to private corporations.

In the hands of profit-seeking drug firms, the time-limited market exclusivity conferred by patents shapes not only the process of scientific discovery and medical innovation, but also their approach to pricing and marketing.

Consistently one of the most profitable sectors, the pharmaceuticals industry is under pressure to maintain high returns. Not surprisingly, this translates into prioritising classes of drugs which are likely to generate large streams of revenue with low levels of R&D investment, rather than prioritising medicines of high public health priority. As a result, 'me too' drugs for chronic diseases take priority over novel treatments for acute illnesses. The improvement of a 'me too' drug may only be marginal over existing therapies, but a consumer buying a chronic-disease drug for years returns far more revenues than a short antibiotic course.

Tropical diseases remain neglected while lifestyle medications receive priority in the R&D pipeline. Though tropical diseases may impose a far greater burden of disease, these neglected diseases often afflict resource-poor markets from which patents can extract little in the way of profits. Under the current system of financing pharmaceutical R&D, public health and private-sector priorities have become misaligned.

The wish to generate high revenue streams also incentivises pharmaceutical companies to spend large amounts on advertising, marketing and influencing the prescribing behaviour of doctors, to downplay considerations of safety, and to set prices to maximise revenue rather than access.

Finally, and equally troubling, R&D productivity has fallen over the past decade: industry R&D expenditures have gone up 147 per cent from 1993 to 2004 while the approval of new chemical entities by the US Food and Drug Administration dropped from a peak of 53 new molecular entities in 1996 to 18 in 2007 (GAO 2006; Jordan 2008). To maintain this R&D premium, the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) reports that the industry spent $51 billion in 2005, which amounts to less than 9 per cent of global sales (IFPMA 2006; IMS Health 2005). Most of the R&D premium is recouped in the industrialised

IMAGE B5.1 **A vendor sells pharmaceuticals at a street market in Senegal**

world. The pharmaceuticals market of the developing world, by value, amounts to only 8.8 per cent (WHO 2004a). What type of R&D, though, does this system buy?

Existing strategies for overcoming financial barriers to access

A variety of strategies are used to overcome the barriers to access caused by the high price of medicines. These include promotion of the use of differential pricing schemes (tailoring the price of medicines to the differential purchasing power of different countries); voluntary licences (where patent holders voluntarily award a licence to a manufacturer to produce a patented medicine at a lower price); and corporate social responsibility approaches such as making drug donations or selling medicines at a discount.

Public strategies include governments issuing compulsory licences to get around the monopoly pricing of patented drugs. Another has been to allocate more public and donor money to purchase medicines on behalf of poor people. Various public–private partnerships have also been developed, often involving public finance, United Nations agencies, private companies and

non-profit, non-governmental organisations (NGOs), to develop new and affordable medicines and other health technologies. Partnerships, as well as the use of Advance Market Commitments (AMCs), have also been encouraged as a strategy for addressing the gaps in R&D for neglected diseases.

Finally, poor people also implement their own strategies. These include diverting household income from food to medicines, taking children out of school, and selling off what little assets they have. They may also resort to purchasing cheaper medicines on the informal market, exposing themselves to fraud and harm.

But the strategies described above, even collectively, do not provide an adequate or equitable response to the problem of inaccessible medicines. And none of them addresses the fundamental problems of a system based on patents and profit-seeking behaviour.

A new system for financing and rewarding pharmaceutical R&D

Over the last few years, efforts have been made by various academics and civil society groups to develop a strategy that would overcome the flaws in the current system. In 2003, the WHO's Commission on Intellectual Property, Innovation and Public Health (CIPIH) was established to review existing medical R&D efforts and intellectual property regimes, and to consider other incentive and funding mechanisms for stimulating R&D.

However, at the time of its establishment, the US government and the pharmaceuticals industry lobbied to prevent the CIPIH from considering any amendments to existing international legal or trade instruments, or to consider suggestions that had been made for an international R&D treaty. As a result, a diverse group of NGOs, academics and health experts decided to formulate and draft the outline of a possible R&D treaty. In February 2005, 162 individuals petitioned the WHO Executive Board and the CIPIH to formally evaluate the draft treaty.[1]

The treaty was based on the idea that governments should spend a certain proportion of national income on medical R&D and that there would be maximum sharing of any knowledge and technology that would emerge from this public investment. The treaty became an issue of great debate within the CIPIH. When the Commission published its final report in April 2006,[2] it noted the need for sustainable sources of finance into R&D for neglected diseases and said that the proposed international R&D treaty provided some new ideas that deserved further discussion.

Meanwhile, Kenya and Brazil had been leading a process to introduce a resolution to the World Health Assembly (WHA) on the creation of a 'Global Framework on Essential Health Research and Development'. In spite of attempts to have this blocked, resolution WHA 59.24 was adopted in

May 2006 incorporating several recommendations made by the CIPIH and by Kenya and Brazil. It also called for the establishment of the Intergovernmental Working Group on Public Health, Innovation and Intellectual Property (PHI/IGWG).

PHI/IGWG was tasked with drawing up a global strategy and plan of action to secure, inter alia, an enhanced and sustainable basis for needs-driven, essential health R&D. Its first meeting took place in December 2006. In February 2006, Bangladesh and Bolivia submitted papers to PHI/IGWG calling for consideration of new methods of stimulating medical R&D in which incentives for stimulating innovation are separated from the prices of medicines, such as the use of prizes.

What's the big idea about prize funds?

The proposal that 'prize funds' be used as an alternative method for financing and rewarding successful investments in R&D has been addressed in detail by, among others, the NGO and think-tank Knowledge Ecology International (KEI).[3]

Prize funds are basically a way of providing an alternative reward to innovators – one that is not linked to the sale and price of the product. Instead, innovators would be rewarded on the basis of the contribution they make to improving health outcomes. Clearly, an important requirement of prize funds is the generation of finance for the fund and a system to adjudicate the value of the innovation or invention.

Prize funds could, however, exist together with patents. But patents would be used to make a claim against a monetary prize, rather than an exclusive right to make, market or use an invention. By divorcing the incentive for innovation from the product's price to consumers, outputs of the R&D could be placed in the public domain immediately, so that competition among manufacturers and suppliers would lead to low prices and more efficient medical innovation. It would also promote rational drug use and reduce spending on unimportant 'me too' products that do not improve health outcomes and curb spending on marketing.

The idea of prize mechanisms to stimulate R&D will require effort and political will. But there are some starting points. For example, a proposed US Medical Innovation Prize Fund would reward successful drug developers with monetary prizes, not a temporary monopoly. Each new successful drug would qualify for prize money, the amount of which would depend upon the overall size of the fund and evidence of the incremental impact of the new product on health outcomes. While every new product would be a 'winner', they would also compete against each other for a share of the total prize fund.

Another proposal involves the special case for medicines that rely on money from donors. The suggestion is that donors would set aside a fixed proportion (e.g. 10 per cent) of their existing budget for drug purchases to finance a prize fund. However, prizes would only be available to patent owners who agree to license their patents to a shared patent pool. Manufacturers could then compete to produce generic versions of the medicines in the patent pool. The patent owners would be rewarded according to the positive impact of their inventions on health outcomes in developing countries.

A precedent for the use of prize funds is the 2005 Grainger Challenge, which involved prizes of up to US$1 million for the development of cheap filtration devices for removing arsenic from well water. Over seventy entries were submitted. The winning entry, announced in 2007, is now being used to provide safe drinking water to hundreds of thousands of people. Less successful was the 1994 US$1 million Rockefeller Prize for developing a low-cost diagnostic test for gonorrhea or chlamydia. The prize expired in 1999 without a winner.

Prize mechanisms are not a magic-bullet solution to the inequities and inefficiencies of the pharmaceuticals sector. Neither do they address the low levels of technical capacity in low- and middle-income countries. Unless such capacity is developed, it will mainly be established pharmaceuticals companies that are able to compete for the prize funds. Prize mechanisms therefore need to be seen as part of a larger set of systems and incentives that includes direct or indirect government funding of basic research, non-profit product development partnerships (PDPs) and technology transfer agreements. What prize funds offer uniquely is an alternative to the marketing monopoly as an incentive for private investment.

Meeting the challenge of antibiotic resistance: public good and collective action[4]

Antibiotic resistance represents another illustration of the current failings of the pharmaceuticals sector as well as a neglected public health priority in its own right. Although the intensity of antibiotic use is greatest in industrialised countries, the burden of infectious disease falls disproportionately on developing countries where national strategies to contain antibiotic resistance are often absent and where there is a general lack of access to reserve antibacterials (Fasehun 1999; WHO 2004b).

Antibiotic resistance recognises no geographic boundaries. Last year, global media tracked the story of a plane passenger who purportedly had multi-drug-resistant tuberculosis (MDR-TB), but who had managed to

trek across Europe and Canada on his return to the United States while untreated and infectious (CNN 2007).

Less widely reported is the fact that XDR-TB (extensively drug-resistant tuberculosis) has been identified in every region of the world, most frequently in the former Soviet Union and in Asia (WHO 2006). During the 1990s, a resistant strain of *Streptococcus pneumoniae* spread worldwide from Spain (Smith and Coast 2002).

Within countries, antibiotic resistance is no longer a problem primarily found in hospital wards, but has extended into the community. Increasingly, transmission of community-acquired, multi-drug-resistant infections is occurring in developing countries (Okeke et al. 2005).

Strategies to counter resistance can be divided between those that conserve the effectiveness of antibiotics and those that replenish the supply of new drugs. To conserve the effectiveness of antibiotics, steps can be taken to reduce infections in the first place, delay the emergence of resistance, and slow its spread. To replenish the supply of new antimicrobials, the R&D pipeline for new drugs, or, better still, new classes or mechanisms of antibiotic therapy, needs to be primed with new drug candidates and financed.

Ensuring the effectiveness of antibiotics involves tackling both underuse and overuse. Underuse stems from problems of therapeutic, financial and structural access. The lack of therapeutic access refers to the failure of the R&D pipeline to produce appropriate drugs or drug combinations. The lack of financial access arises from unaffordable prices, and can result in patients truncating a full treatment course, thereby facilitating the emergence of resistance. Finally, limited resources might prompt procurement agencies to opt for less costly therapy at the expense of more appropriate therapy. An example from a related area is the use of quinine therapy or artemisinin monotherapy when, in fact, artemisinin combination therapy would work most effectively in the face of growing malarial resistance.

Problems of structural access can take various forms. Antibiotic overuse also hastens the emergence of resistance. Overuse might take the form of using an antibiotic when not necessary or using an overly broad-spectrum antibiotic for a narrow clinical indication. Various reasons contribute to overuse (Elamin 2003). Typically, overuse mitigates risks perceived by the health provider – risks of missing a treatable diagnosis, losing a patient in follow-up, or incurring the costs of return visits. Health providers may opt for presumptive therapy when rapid diagnostics are not available, handing out prescriptions to meet patient expectations and substituting antibiotic treatment for clinic visit time (Schartz 1997). As resistance grows, so might the perceived need for broad-spectrum antibiotics in a vicious feedback loop.

Together, underuse and overuse of antibiotics are rampant. WHO (2004b) estimates that 'more than half of medicines are prescribed, dispensed or sold inappropriately' and 'half of all patients fail to take [medicines] correctly'. As much as 20–50 per cent of antibiotic prescriptions in community settings and 25–45 per cent of antibiotic prescriptions in hospital settings may be unnecessary (Hooton 2001). Irrational drug prescribing has been noted for decades but still receives cursory policy attention.

Antibiotic resistance both removes therapeutic options and imposes significant economic costs. Treatment alternatives may no longer work, or their effective market life may be shortened. The impact, however, extends to other life-prolonging and life-saving technologies reliant on the complementary use of antibiotics. Antibiotic resistance places many advances of modern medicine, ranging from organ transplants to cancer chemotherapy, in jeopardy. Measuring the economic toll of antibiotic resistance is methodologically complex, but significant by any measure. Indeed, estimates of the costs to the US alone range from $350 million to $65 billion (Foster 2007; Laxminarayan et al. 2007).

Conserving the effectiveness of antibiotics

The preservation of effective antibiotic therapy is a typical public good (Smith and Coast 2003). The two defining characteristics of a public good are non-rivalry (where consumption by one person does not limit or diminish access to the good by the next person) and non-exclusivity (where access to the good cannot be restricted, and therefore is available to everyone). Examining each dimension provides insight into the problem of containing antibiotic resistance.

In so far as the benefits of new antibiotics are beyond the financial reach of those in developing countries, the benefits are excludable. In so far as the benefits extend beyond the individual's consumption, the lower risk of communicable disease is community-wide and thereby non-exclusive. Like vaccines, the use of antibiotics can reduce the spread of contagion. Unlike vaccines, no herd immunity results, and any public benefit is mostly local and transitory.

The containment of antibiotic resistance, however, can be both non-excludable and non-rival. This leaves open the possibility of a *tragedy of the commons*, which arises when the gains for individuals impose costs on the community collectively (Hardin 1968). Antibiotic resistance pits the micro-motives of particular stakeholders against those of the entire community. This tension plays out at multiple levels between physician and patient, hospitals and health insurers, and drug companies and health insurers.

In the face of diagnostic uncertainty, the physician minimises risks to the individual patient and reaches for presumptive therapy. To order a further diagnostic test would likely involve more money and greater delay. A timely start to treatment may improve the likelihood of clinical success. Imprecise diagnostics contribute to the use of broader-spectrum antibiotics. That uncertainty in clinical decision-making also extends to variations in the prescribed duration of antibiotic therapy.

If vaccines were available, the physician would not face this dilemma and the need for antibiotics would be reshaped. For example, pneumococcal conjugate vaccine prevents 35 antibiotic prescriptions per 100 children, with savings estimated at 1.4 million antibiotic prescriptions in the United States each year by reducing the incidence of otitis media (Fireman et al. 2003). Importantly, a study in South Africa demonstrated that the carriage of antibiotic-resistant strains may decline after vaccination (Mbelle et al. 1999).

The financial incentives facing hospitals may provide no incentive for tackling antibiotic resistance if all they see are beds filled for longer hospital stays and corresponding payments. Infection control measures such as hand hygiene are investments that no single insurer would make if they imposed higher operating costs and encouraged freeriding by other insurers. Among hospitals serving the same catchment area, there may be little incentive to undertake aggressive infection control measures.

In the Netherlands, a strict containment approach to methicillin-resistant *Staphylococcus aureus* (MRSA) has kept prevalence below 0.5 per cent in contrast to higher rates of 1.6 per cent to 62.4 per cent in neighbouring Belgium (Verhoef et al. 1999). Not only were patients infected with MRSA isolated, but all health-care workers in contact with that patient also are swabbed regularly. In fact, all patients from outside the Netherlands undergo quarantine for forty-eight hours or until three successive tests come back negative for MRSA. Although this policy cost €2.8 million, it was estimated to be half the anticipated cost that might have otherwise resulted from MRSA and related infections (Vriens et al. 2002).

At the market level, there is a trade-off between the rapid scaling up of antibiotic use and the emergence of resistance. Rapid scaling up might ramp up pharmaceutical revenues, but rapid emergence of resistance might shorten the period that an antibiotic remains effective. Modelling suggests that antibiotics marketed aggressively at the outset of entry into the health system return lower revenues than those gradually introduced to reduce the emergence of antibiotic resistance (Power 2006). However, the reality is that there are many existing antibiotics in the marketplace, and with competition within a therapeutic class there is little incentive for any single manufacturer to exercise restraint in marketing the use of an antibiotic.

Replenishing the supply of antibiotics

Between the 1930s and 1970s, over a dozen new classes of antibiotics entered the marketplace. However, in the last four decades, only two new classes have surfaced (IDSA 2004). Only thirty-one anti-infective drugs are currently under development among the top fifteen multinational pharmaceuticals companies (Spellberg et al. 2004). Among these, only five are antibacterials (comprising only 1.6 per cent of the publicly disclosed pipelines of these companies), none of which appears to have a novel mechanism of action. Adding the seven largest biotechnology companies to this analysis did not improve the outlook.

A more in-depth analysis of the entire industry in 2005 provides a clearer picture. White (2005) found seventy drug candidates in the pipeline, thirteen of which were in five new classes of antibiotics. Of the forty-four candidates whose bacterial targets were known, most were for Gram-positive bacteria. Additionally, all the drug candidates for new classes of drugs – where targets were disclosed – targeted only Gram-positive and respiratory-tract bacteria. There were no new class candidates for Gram-negative bacteria.

Companies set R&D priorities according to the net present value and a measure of expected revenue for R&D investment. Antibiotics have a low net present value compared to many other types of therapy (Projan 2003; Projan and Shlaes 2004), due in part to shorter treatment length compared to chronic therapies, high therapeutic competition, the restriction of use of new antibiotics to resistant infections, and decreased value due to the emergence of resistance (Charles and Grayson 2004).

Mobilising for solutions

Combating antibiotic resistance has generated lengthy lists of proposed policy interventions (Laxminarayan et al. 2007; WHO 2005; Smith and Coast 2003). While more research may be needed to develop new and effective antibiotics, action plans can build on the ample evidence base for prevention and containment. More importantly, mobilising for change involves strategic choices. These choices should prioritise pathways that:

- make data actionable;
- reframe antibiotic resistance as a cross-cutting concern;
- realign incentives by pooling risks, resources and response;
- re-engineer the value chain of R&D for new diagnostics, drugs and vaccines.

To make data actionable, one has to motivate its collection. Access to over-the-counter drugs, unnecessary presumptive treatment and weak regulatory systems hinder efforts to bolster rational use of antibiotics.

Though some parts of the world track antibiotic resistance patterns (e.g. the European Antibiotic Resistance Surveillance System), most regions do not have effective surveillance systems in place. Improved data collection is also important for mobilising action and monitoring efforts to improve clinical practice. At the country level, such steps may help spur and revitalise rational prescribing programmes, use of essential drug lists, and other activities by ministries of health.

In the US, for example, the Institute for Healthcare Improvement launched the 100,000 Lives Campaign to reduce preventable deaths in US hospitals. The campaign targeted six best-practice interventions, including the prevention of infections at central line and surgical sites. By setting quantifiable goals and targets, and developing a methodology for counting the number of lives saved, the Campaign and more than 3,000 participating hospitals were able to achieve remarkable success. Building on this, the '5 Million Lives Campaign' is now under way to prevent 5 million incidents of iatrogenic harm in the US.[5]

The example demonstrates how making antibiotic resistance a cross-cutting concern may give it greater traction. Through a campaign aimed at improving patient safety in the hospital, infection control measures might be implemented, which in turn makes the environment less conducive to the development of antibiotic resistance. Extending the approach further, the World Alliance for Patient Safety has set its sights on campaigning to combat antibiotic resistance, building upon the stepping stones of previous efforts to improve hand hygiene and safe surgery.

Antibiotic resistance is an issue that cuts across AIDS, tuberculosis and malaria programmes. Lessons learned about surveillance and syndromic management, for example, might apply across these programmes. By coordinating these efforts, the WHO might develop synergy among these vertical disease programmes and lead by example on these issues.

Another strategic approach involves the pooling of health financing and health risks in order to improve the rational use of drugs. For example, a competitive health insurance market creates weak incentives for insurance companies to motivate infection control in local hospitals. But if the patients going to hospitals belong to the same health insurance pool, then the individual health insurance company internalises these costs and has a stronger incentive to act. By apportioning costs that otherwise might fall as an externality on others, policies that pool resources among these stakeholders share the burden of supplying a public good.

Finally, what about R&D for new antibiotics and complementary technologies like diagnostics and vaccines? There are multiple points along the value chain of R&D that would benefit from re-engineering. Various

groups have called for applying a range of financial incentives to encourage drug manufacturers to develop new antibacterial drugs (Laxminarayan et al. 2007; IDSA 2004; Spellberg et al. 2007). In addition to changing the nature of financing and incentives, there is a need to rethink the opportunity costs, economies of scale and profit expectations.

For example, by working with manufacturers in emerging economies, academia has the potential to change the value chain of drug R&D more fundamentally. Sunil Shaunak and his colleagues at Imperial College in London recognised that the treatment for hepatitis C was too expensive for widespread use in the developing world. When they modified pegylated interferon to make it last longer and work better in tropical climates, they created a company, PolyTherics, to handle the new product and then licensed the drug directly to a company in India to conduct the clinical trials and to make the product available at a target $3/dose, much lower than the current $200/dose. The deal does not generate as much revenue for PolyTherics on a per unit basis, but it does illustrate a model of partnership between academia and developing-country drug manufacturers that enables more affordable access in poor countries.

Firm size and cost of operations appear to be important as well. Manufacturers with lower overhead costs might be more willing to serve markets where the profit margin is tighter. Where the big drug companies may not find markets attractive, universities or smaller companies in developing countries may step in. For example, after losing money on the tuberculosis drug Seromycin, Eli Lilly transferred rights on the drug to Purdue University. Purdue believes that its lower overheads and smaller capacity will allow it to manufacture this drug without suffering losses, and this will make Purdue the only supplier of Seromycin in North America (Purdue 2007).

The R&D of new diagnostics also requires attention. The basic technique for diagnosing TB has evolved little in over a hundred years and remains complicated and costly. Simplifying and streamlining the process would mark a significant advance. For other infectious diseases like malaria, paediatric diagnostics alone could prevent approximately 400 million inappropriate treatments every year (Global Health Diagnostics Forum 2006). Point-of-care diagnostics for bacterial infections could help reduce the clinical uncertainty that results in unnecessary, presumptive treatment of patients with antibiotics and improve care. Rapid diagnostics for the detection of bacterial pathogens in food also could reframe how policymakers handle food safety and trade. Importantly, moving from the detection of antibiotic residues in food to the finding of antibiotic-resistant plasmids in poultry and livestock products could bolster efforts to limit the inappropriate use of antibiotics in animals.

Conclusion

The victims of antibiotic resistance are too often faceless. As with other public goods, combating antibiotic resistance will require effective governmental, civil society and private-sector efforts. Policy interventions have to change the rules of the game. Surveillance has to be redesigned to create actionable, follow-on steps. The issue of antibiotic resistance has to be reframed to be a problem of more than just the community focused on infectious diseases. Pooling can help realign incentives and enlist key stakeholders to contribute to the public good of preventing and stemming the emergence of antibiotic resistance. Re-engineering the R&D and delivery of antibiotics offers some creative pathways forward. The challenge of antibiotic resistance has the form of a repeated game, but only through the spirit of public-sector collective action will humankind go the distance and ensure a future with effective antibiotics.

Taking concerted action, ReAct, a coalition to combat antibiotic resistance, has emerged to tackle this challenge. The coalition's vision is that current and future generations of people around the globe should have access to effective treatment of bacterial infections as part of their right to health.

Notes

1. See www.cptech.org/workingdrafts/rndsignonletter.html.
2. See www.who.int/intellectualproperty/report/en/index.html.
3. See www.keionline.org for more information.
4. This discussion of antibiotic resistance draws upon an abbreviated version of A. So and C. Manz, Meeting the challenge of antimicrobial resistance: Public good and collective action, www.react-group.org.
5. See www.ihi.org/IHI/Programs/Campaign for more information on the campaign.

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