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3Rs for innovating novel antibiotics: sharing resources, risks, and rewards

The stream of new antibiotics is struggling to keep up with emerging bacterial resistance. **Anthony So and colleagues** examine what can be done to increase innovation

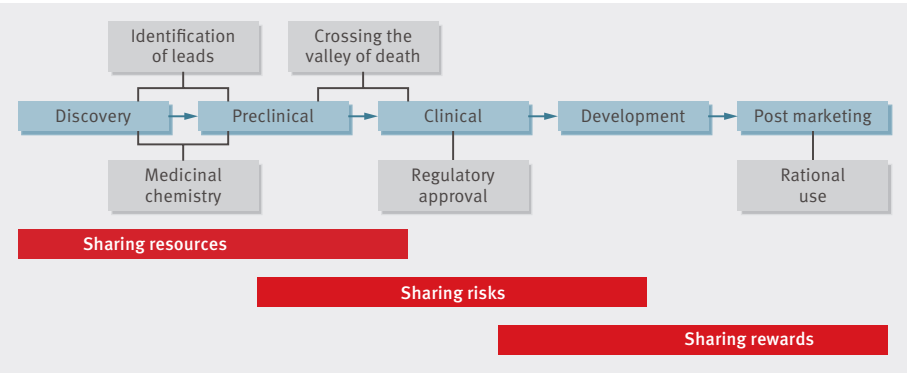
The dearth of novel antibiotics poses challenges to the treatment of bacterial infection and points to shortcomings in the system of pharmaceutical innovation. Increasing bacterial resistance to existing antibiotics causes substantial morbidity and mortality and threatens society's ability to realise benefits from modern medical advances. Access to effective antibiotics is essential to treating the unavoidable infections that come with cancer chemotherapy, organ transplantation, or the care of premature babies.

Yet studies have repeatedly confirmed the faltering research pipeline for novel antibiotics and cited the exit of major pharmaceutical firms from this therapeutic area. In the publicly disclosed pipelines of the top 15 drug companies, only five drug candidates, or 1.6% of the pipeline, were antibiotics.[1] A more comprehensive search of two commercial databases also turned up few novel antibacterial drug candidates.[2] Of the 15 candidates identified that could be administered systemically, only four were active against Gram negative bacteria, two of which acted on new targets; none of the four had a novel mechanism of action.[2]

With few promising drug candidates in sight, the near term prospects of new antibiotics are dismal.[3] The bottlenecks in bringing a novel antibiotic to market span from discovery to delivery (fig 1). Upstream in the research and development pipeline, concerns have surfaced over identification of leads and medicinal chemistry. Especially critical is the step between preclinical and clinical development (the "valley of death"). Drug companies have been hesitant to take compounds into large and costly clinical programmes because of the uncertain return on investment and academic researchers and smaller companies find it difficult to get venture capital for clinical research. Downstream, concerns over the regulatory approval process have stirred debate, and financing research and development may also pose barriers.

Drug companies have to see that their expected returns will exceed the costs of research and development. But compared with other therapeutic categories, the economic value of antibiotics to pharmaceutical firms is considerably lower.[4] Research into antibiotics therefore often loses out to potentially more lucrative health technologies.

Possible interventions to improve the pipeline have been identified.[5 6] But identifying which is the inspired solution is not easy. Nor is there likely to be a single solution. Effective solutions are likely to include sharing the three Rs—resources, risks, and rewards..



Bottlenecks in the antibiotic pipeline

Sharing resources

The availability of resources—particularly research inputs—is important in tackling challenges to drug discovery. Although the range of promising targets is not a primary limiting factor, existing compound libraries and the methods used to mine them have not identified sufficient drug candidates. GlaxoSmithKline garnered just five leads from 70 automated high throughput screens conducted between 1995 and 2001—a yield fourfold to fivefold lower than for other therapeutic areas.[7]

It is questionable whether further mining of existing libraries will ever produce more positive results. Other strategies that might increase yields include enriching collections with natural products, fragment based screening, additional work on parts of the genome thought to be less easily druggable, and structural genomics.[8] Part of the problem may lie in the emphasis on "rational" drug development focused on single targets and high throughput screening. We need to get back to the basics of biology—"targeting an organism (bacterium) inside another organism (the human host)"—and give more attention to the potential of resistance arising rapidly.[9]

In addition, limited access to medicinal chemistry resources may hinder the development of leads. Medicinal chemistry is needed to determine the pharmacokinetic properties; structure-activity relationship; absorption, distribution, metabolism, and excretion; and safety profile.[10] Smaller firms or academic research groups might benefit from centralised access to contracted medicinal chemistry services.

Sharing resources might allow a greater diversity of groups to search for novel antibiotics. With support from the Medicines for Malaria Venture, GlaxoSmithKline released the chemical structures and assay data for 13 500 compounds it had identified as having antimalarial activity against *Plasmodium falciparum*. The information was deposited in the European

Bioinformatics Institute's freely available ChEMBL database and the US National Institutes of Health (NIH) PubChem database. Various models have sought to broker similar access to data that remain proprietary. The European Rare Diseases Therapeutic Initiative focuses on enabling academic research teams to access proprietary compound libraries for preclinical studies of rare diseases.[11] The Special Programme for Research and Training in Tropical Diseases has also secured access to the compound libraries of Merck Serono and Pfizer.[12] These arrangements have provisions in common, including a layer of confidentiality, the option of first refusal, and potential access to proprietary data. Of note, similar collaborative strategies have been proposed for companies seeking access to small molecules of potential commercial value, not just those for rare or neglected diseases.[13]

While companies might once have balked at sharing information that could advantage competitors, the line between precompetitive and competitive data has shifted downstream, leading to unprecedented collaborations. The need for better treatments for neurodegenerative diseases, notably Alzheimer's and Parkinson's disease, led the Coalition Against Major Diseases to develop common clinical data standards and a pooled database of control groups in clinical trials from multiple companies.[14]

Building the public infrastructure for compound libraries and their screening might complement access to proprietary collections. One such example is the NIH Molecular Libraries Probe Production Centers Network.[15] Structural information on compounds deposited in the Molecular Libraries Small Molecule Repository and screening data generated has become publicly available in PubChem. By overcoming scientific challenges, such sharing of resources helps to reduce the risks of research and development.

Sharing risks

Sharing the risks of research and development across public and private sectors eases the transition from preclinical to clinical testing. Public sector support is already accelerating development of treatments for rare diseases. For example, in the US, the Therapeutics for Rare and Neglected Diseases programme uses NIH's intramural resources to bring drug leads forward to meet FDA requirements for an application for an investigational new drug. By contrast, the Bridging Interventional Development Gaps programme allows those developing new drugs to compete for services, contracted by the government, for formulation of good manufacturing practices, animal toxicology, and development of assays for pharmacokinetic testing. Applied to antibiotics, such services might well boost the success of preclinical research and development. NIH has opened the National Center for Advancing Translational Sciences, which will consolidate such efforts to fill research gaps.[16]

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Disease specific, patient driven foundations have also had an important role in developing collaborative research. In the US, the Cystic Fibrosis Foundation's therapeutics development network has linked 18 national research centres. Together they have conducted over 40 clinical trials—including several on antibiotics—involving 4700 patients (more than a sixth of people with the disease in the United States).[17] They have also developed improved trial protocols and standardised endpoints, driving forward the search for new cystic fibrosis treatments despite the relatively small market.

Public funding could provide a platform for innovation. India's Council for Scientific and Industrial Research provided government funding for the Open Source Drug Discovery project in which hundreds of volunteer scientists and students at universities collaborated online to re-annotate the *Mycobacterium tuberculosis* genome. The volunteers completed many person-years of work in just four months.[18] Regional innovation platforms such as the African Network for Drugs and Diagnostics Innovation (ANDI) have also emerged, along with sister networks in Asia and America, to leverage existing research capacity and open doors to South-South collaboration.[19]

Government and philanthropic funding for antibiotic research is being made available to a growing range of actors. The US Department of Defense has awarded contracts to companies including GlaxoSmithKline's Antimicrobial Resistance Center for Excellence in Drug Discovery and Trius Therapeutics.[20 21] The US Department of Health and Human Services' Biomedical Advanced Research and Development Authority (BARDA) has supported Achaogen for developing a broad spectrum antibiotic to treat bioterrorism threats from plague, tularaemia infections, and drug resistant pathogens.[22] In the UK, the Wellcome Trust has developed a broad portfolio of antibiotic projects, providing grants for small firms with promising early stage novel chemistry through its seeding drug discovery programme as well as funding for translational research to bring innovative treatment technologies closer to market.[23] In seeking greater collaboration between the public and private sectors, the European Commission's Innovative Medicine Initiative is considering antibiotic resistance as a topic for 2012.[24] However, ensuring fair returns on these public and philanthropic investments requires that society share in the rewards.

Sharing rewards

The average antibiotic approved between 1990 and 1994 had an economic value to a pharmaceutical firm of $2.4bn over a 20 year product life cycle, substantially less than the $4.2bn for central nervous system drugs and $3.7bn for cardiovascular drugs.[25] In 2009, the worldwide sales of central nervous system drugs were still nearly double the value of antibacterial drug

sales—and those of cardiovascular drugs were over three times the value.[26-28] Over the past five years, the antibiotics market registered only 4% annual growth while antiviral drugs and vaccines exceeded 16%.[29] Clearly antibiotics are less commercially attractive to companies than many other drugs, but any financial incentive to bring novel antibiotics to market must ensure that their use is safe, rational, and affordable to those in need.

Many incentives reliant on market exclusivity tie financial returns to sales rather than rational and affordable use. Some have sought to mitigate these shortcomings with proposals for broad patents over groups of antibiotics that compete for effectiveness[30] and value based reimbursement that is dependent on meeting drug conservation targets.[31] US legislative initiatives like the Generating Antibiotic Incentives Now (GAIN) Act unfortunately mainly use data exclusivity in the hope that extending the monopoly protection on novel antibiotics to treat multidrug resistant infections will give companies added incentive.[32] However, industry, at least in Europe, increasingly acknowledges the need to delink incentives from sales of the product.[33] Proposals range from conditioning public funding with fair returns on research and development to buying out patents so that manufacturers can be licensed to produce antibiotics on a scale appropriate for rational use. For antibiotics, the existing imbalance between excess use and lack of access must also be addressed through optimal production volumes, controlled distribution, and rational use.

If public funds are invested in research and development it is fair to insist on sharing some of the rewards. Product development partnerships for antibiotics may ensure both fairer returns on public investment and more affordable pricing, as has been achieved by the Drugs for Neglected Diseases Initiative for antimalarial fixed dose combination drugs.[34]

Conclusions

The way forward will involve a dynamic mix of public-private partnership with solutions that tackle both scientific and financial bottlenecks in the pipeline. Sharing resources, risks, and rewards each suggest operating principles against which to benchmark potential solutions. For starters, sharing resources should extend the bounds for exploratory research and shift the line between precompetitive and competitive information. Sharing risks should extend public sector science and build infrastructure for collaborative research and development, and sharing rewards should delink financial returns from sales of the product and ensure fair returns for the public sharing of risks in investing in research and development. Importantly, the 3Rs should not be considered in isolation, but coordinated in an integrated approach. For example, resources from the NIH's National Center for Advancing Translational Sciences, the European Union's Innovative Medicines Initiative, and other funders might result in a coordinated platform for accelerating antibiotic innovation, both sharing resources and risks. Public sector capital invested in antibiotic innovation might be structured in a way to lower the costs of private sector capital investments and also ensure fair returns to the public. Finding the right strategic mix of approaches remains the challenge ahead.

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1 Spellberg B, Powers J, Brass E, Miller L, Edwards J. Trends in antimicrobial drug development: implications for the future. *Clin Infect Dis* 2004;38:1279-86.
2 Aronsson B, Boscan IS, Cars O, Giamarellou H, Gyssens IC, Lutsar I, et al. The bacterial challenge: time to react. European Centre for Disease Prevention and Control and European Medicines Agency joint report. 2009 www.ema.europa.eu/pdfs/human/antimicrobial_resistance/EMEA-576176-2009.pdf
3 Hamad B. The antibiotics market. *Nature Rev Drug Discovery* 2006;9:675-6.
4 Projan SJ. Why is big pharma getting out of antibacterial drug discovery? *Curr Opin Microbiol* 2003;6:427-30.
5 Mossialos E, Morel C, Edwards S, Berenson J, Gemmill-Toyama M, Brogan D. Policies and incentives to promote innovation in antibiotic research. Final report 2010. www.euro.who.int/__data/assets/pdf_file/0011/120143/E94241.
6 Kesselheim A, Outterson K. Fighting antibiotic resistance: marrying new financial incentives to meeting public health goals. *Health Aff* 2010;29:1689.
7 Payne D, Gwynn M, Holmes D, Pompliano D. Drugs for bad bugs: confronting the challenges of antibacterial discovery. *Nature Rev Drug Discovery* 2007;6:29-40.
8 Schmid M. Seeing is believing: the impact of structural genomics on antimicrobial drug discovery. *Nature* 2004;2:239.
9 ReAct. Collaboration for innovation—the urgent need for new antibiotics. ReAct policy seminar, 23 May 2011, Brussels, Belgium. www.reactgroup.org/uploads/news/Collaboration-for-Innovation-The-Urgent-Need-for-New-Antibiotics-ReAct-Policy-Seminar-Brussels-May-23-2011.pdf.
10 Bleicher K, Bohm H, Muller K, Alanine A. Hit and lead generation: beyond high-throughput screening. *Nature Rev Drug Discovery* 2003;2:369.
11 Fischer A, Borensztein P, Roussel C. The European rare diseases therapeutic initiative. *PLoS Med* 2005;2:e243.
12 Nwaka S, Ramirez B, Brun R, Maes L, Douglas F, Ridley R. Advancing drug innovation for neglected diseases—criteria for lead progression. *PLoS Negl Trop Dis* 2009;8:e440.
13 Rai AK, Reichman JH, Uhlir PF, Crossman C. Pathways across the valley of death: novel intellectual property strategies for accelerated drug discovery. *Yale J Health Law, Policy, Ethics* 2008;8:53-89.
14 Coalition Against Major Diseases. www.c-path.org/CAMD.cfm
15 Austin C, Brady L, Insel T, Collins F. NIH molecular libraries initiative. *Science* 2004;306:1138.
16 Collins F. Reengineering translational science: the time is right. *Science Transl Med* 2011;3:90:90cm17. www.nih.gov/about/director/articles/translational_science_07062011.pdf.
17 Goss C, Mayer-Hamblett N. The Cystic Fibrosis Foundation therapeutics development network: a national effort by the Cystic Fibrosis Foundation to build a clinical trials network. *Children's Health Care* 2008;37:5-20.
18 Ghosh S. How the young brigade mapped the TB genome. *The Hindu* 2010. http://beta.thehindu.com/sci-tech/article397395.ece.
19 Nwaka S, Ilunga T, Da Silva J, Verde E, Hackley D, Vre R, et al. Developing ANDI: a novel approach to health product R&D in Africa. *PLoS Medicine* 2010;7:e1000293.
20 GlaxoSmithKline. GlaxoSmithKline awarded US Department of Defense contract to pursue novel antibacterial research program. 2007. http://us.gsk.com/html/media-news/pressreleases/2007/2007_09_18_GSK1146.htm.
21 Fikes B. Trius receives $29.5 million contract to find microbe antibiotics. *North County Times* 2010 Sep 20. www.nctimes.com/business/article_bb6141ed-f20b-5016-b00e-96a2bacab749.html.
22 http:///US Department of Health & Human Services. BARDA funds drug development for biothreats, antibiotic resistance. Press release, 30 August 2010. www.hhs.gov/news/press/2010pres/08/20100830a.html.
23 Wellcome Trust. Therapeutics. 2010. www.wellcome.ac.uk/Funding/Technology-transfer/Funded-projects/therapeutics/index.htm.
24 Innovative Medicines Initiative. NewDrugs4BadBugs (ND4BB). www.imi.europa.eu/content/future-topics.
25 DiMasi J, Grabowski H, Vernon J. R&D costs and returns by therapeutic category. *Drug Info J* 2004;38:211-23.
26 BCC Research. Infectious disease treatments: global markets. 2010. www.bccresearch.com/report/PHM061A.html.
27 BCC Research. Therapeutic drugs for central nervous system (CNS) disorders: technologies and global markets. 2010. www.bccresearch.com/report/PHM068A.html.
28 BCC Research. Cardiovascular therapeutic drugs: technologies and global markets. 2010. www.bccresearch.com/report/cardiovascular-therapeutic-drugs-phm024b.html.
29 Hamad B. The antibiotics market. *Nature Rev Drug Discovery* 2010;9:675-6.
30 Laxminarayan R. Antibiotic resistance: can economic incentives play a role? 2001. www.rff.org/RFF/Documents/RFF-Resources-143-antibiotic.pdf.
31 Kesselheim A, Outterson K. Fighting antibiotic resistance: marrying new financial incentives to meeting public health goals. *Health Aff* 2010;29:1689.
32 Govtrack.us. *Text of H.R. 2182: Generating Antibiotic Incentives Now Act of 2011*. www.govtrack.us/congress/billtext.xpd?bill=h112-2182.
33 Bergström R. The role of the pharmaceutical industry in meeting the public health threat of antibacterial resistance. *Drug Resist Updates* 2010;14:77-8.
34 ASAQ: Hope for Malaria. New, once-a-day fixed-dose combination against malaria now available. Press release, 1 March 2007. www.actwithasaq.org/en/press_2.htm.

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Challenges of drug resistance in the developing world

Ramanan Laxminarayan and **David Heymann** examine the factors that make drug resistance a more difficult problem in poorer countries

Resistance to anti-infective drugs, particularly bacterial resistance to antibiotics, is a global phenomenon. Resistant infections increase morbidity and mortality and prolong the time of infectiousness, putting others at risk. In high income countries, where the burden of infectious diseases is modest, the decreasing effectiveness of first line antibiotics is overcome by more expensive second and third line antibiotics. The challenge is greater in developing countries, where the burden of infectious diseases is high and patients with a resistant infection may be unable to obtain or afford any antibiotic, let alone expensive second line treatments. Poor hygiene, unreliable water supplies, civil conflicts, and increasing numbers of immunocompromised people with HIV infection, facilitate both the evolution of resistant pathogens and their rapid spread.[1 2]

The most complete data on resistance in developing countries come from tertiary care facilities, typically located in large cities. Very little information exists on resistance in other settings and almost none in rural areas. Recent data from community settings in Indian and South African urban and peri-urban areas indicate that levels of resistance are high. In urine specimens collected from November 2003 to December 2004, more than 70% of *Escherichia coli* isolated from healthy women were resistant to ampicillin and nalidixic acid, and more than 50% of isolates were resistant to fluoroquinolones (fig 1).[3]

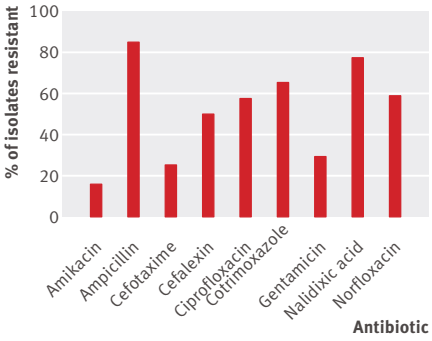

Fig 1 | Antibiotic resistance in *E coli* isolated in New Delhi during 2003-4

Causes of resistance

Increasing use of antibiotics

Bacterial selection for antibiotic resistance is a natural phenomenon related to the volume of antibiotics used: the more these drugs are used the quicker resistant strains emerge and spread.[4] This is true whether antibiotics are medically indicated or not. Antibiotic use is increasing, particularly in Asian and Latin American countries where rising incomes are enabling greater access. The delicate balance in developing countries is between encouraging greater use for appropriate indications—consider the one million deaths of children each year from pneumonia, much of it untreated—and the overwhelming tendency for inappropriate use of antibiotics for coughs, colds, and diarrhoea. In India, per capita antibiotic use increased by 37% between 2005 and 2010, and the fastest growth was in broad spectrum penicillins, cefalosporins, previously unaffordable quinolones, and carbapenems.[5] In low and middle income countries with a high HIV burden, the use of cotrimoxazole to treat opportunistic infections has increased resistance in pneumococci and *E coli*.[6]

There is little incentive for patients or healthcare providers to consider the effect of their decisions to use antibiotics on overall levels of resistance. Some health workers, for example, increase their incomes by selling antibiotics to their patients. In Central China, doctors profit from prescribing and treating insured patients with more expensive antibiotics.[7] Prescribing behaviour in every country is also influenced by medical training and culture and social norms and expectations related to the need for and use of antibiotics.[8]

Institutional incentives may have a role in higher than necessary antibiotic prescribing. In China, many hospitals rely on drug sales for income; one study estimated that a quarter of revenue in two hospitals was derived from

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antibiotic sales.[9] In India, doctors routinely receive compensation from drug sellers in exchange for directing patients to their pharmacies. Insured patients are more likely to be prescribed antibiotics than those without insurance, as they are less affected by cost.[10] Competition from unsanctioned providers also exacerbates competitive pressure on legitimate medical professionals.

Up to 90% of antibiotic use in certain developing countries is over the counter, without a prescription, and non-prescription sales are common in nearly every such country.[11] Despite concern that use of antibiotics without a prescription contributes to resistance, there is little evidence that physicians prescribe antibiotics more appropriately than do trained pharmacists or untrained pharmacy attendants—they all overprescribe, though trained providers may do somewhat better. One reason may be that pharmacists and shopkeepers often mimic prescribing patterns of local healthcare providers and copy both desirable and undesirable practices. A study from Thailand found that a pharmacy's proximity to a hospital improved the appropriateness of antibiotics sold.[12]

Diagnostic tests for infections are commonly unavailable or unreliable in developing countries.[13] In Malaysia, even in hospitals with diagnostic facilities, tests were used in only 20% of cases where it was thought that antimicrobials were indicated.[14] In many countries, diagnostics are still relatively expensive and must be paid for directly by the patient: it is cheaper to use an antibiotic first. Easy to use and inexpensive point-of-care diagnostics could resolve some of these problems, but their development remains a challenge, for technical and economic reasons.

Missed opportunities

Antibiotic use is also driven by missed opportunities to reduce the overall burden of infections. Drug resistance in healthcare settings may be exacerbated by poor infection control and overcrowding of hospitals, particularly public hospitals. A recent point prevalence study of 1265 intensive care units in 75 countries found that 51% of intensive care patients were considered to have an infection and 71% were receiving antimicrobial drugs, some for prophylaxis (somewhat higher than reported in a similar survey in 17 countries in western Europe[15]); most patients were receiving two or more antibiotics.[16] Most hospital acquired infections in low and middle income countries are, as in high income countries, caused by difficult to treat Gram negative organisms.

Low immunisation rates contribute to a high burden of disease that is potentially avertable. In India, less than half of all children are fully immunised with the routine vaccines.[17] Use of the pneumococcal conjugate vaccine (PCV) has lowered infection rates and therefore antibiotic use and resistance in the United States[18 19] but has been adopted in very few low and middle income countries. The association of HIV infection with child serotypes of pneumococci and antibiotic resistance suggests that vaccination could reduce the burden of pneumococcal resistance, making it potentially even more valuable in developing countries.[20 21]

Other causes

Finally, non-human, environmental use of antibiotics is thought to be contributing to selection pressure on resistant strains. In China and Vietnam, demand for meat is driving use of antibiotics to promote growth in poultry and pigs and to keep disease in check where animals are crowded together.[22 23] Environmental contamination with antibiotics or their residues by drug manufacturers in low income countries is a growing problem. Up to 45 kg of ciprofloxacin a day—the equivalent of 45 000 daily doses—was measured in a river close to factories producing this antibiotic.[24] Scientific evidence linking environmental antibiotic selection pressure and resistance in humans remains elusive, but geographical similarities in resistance patterns of human zoonotic and animal infections give reasons to suspect cause and effect.

Consequences of resistance

Despite numerous studies indicating that antibiotic resistance is increasing, little has been done to quantify the attributable burden of resistance in developing countries. The EPIC II study found that infection with multidrug resistant staphylococci, *Acinetobacter* and *Pseudomonas* species, and fungal pathogens was statistically correlated with excess mortality.[16] A study from Thailand found mortality as high as 67% for meticillin resistant *Staphylococcus aureus* and 46% for meticillin susceptible *S aureus*, significantly higher than in high income countries.[25] However, a causal relation between resistance and mortality is difficult to prove because the risk factors for infection with a resistant pathogen, including length of stay in intensive care, are similar to those causing worse outcomes in patients without resistant pathogens. Community based studies have linked chloroquine resistance to increased mortality from malaria,[26] and similar studies are needed to understand the consequences of drug resistance in pneumococci, *E coli*, and staphylococci in developing countries.

Resistance is likely to result in the need for more expensive second line antibiotics, which may be less readily available in developing countries. A recent survey found that the retail price of generic ciprofloxacin, often used as a second line antibiotic, is higher in low and middle income countries than in high income countries, indicating that the economic burden of resistance to first line drugs may be greater in poorer countries (fig 2).

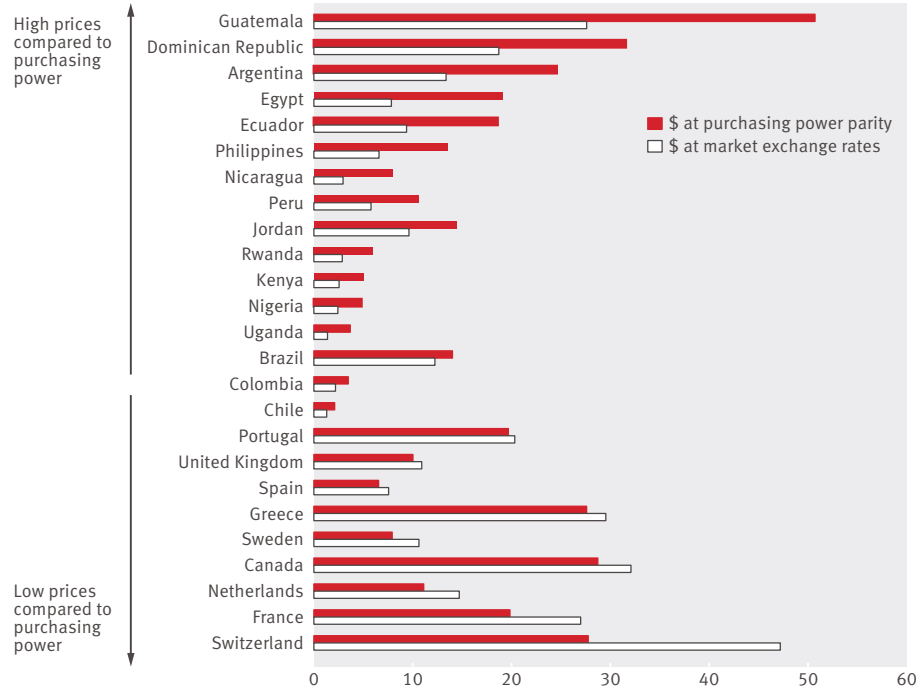

Fig 2 | Cost of course of generic ciprofloxacin (500 mg) in selected countries, 30 November 2009[27]

The way forward

We need to increase awareness among national policy makers in both industrialised and developing countries about controlling antibiotic resistance. The policy goals should be to selectively reduce inappropriate use of antibiotics, increase appropriate use to treat and prevent disease, and reduce the need for antibiotics—a challenge in the context of weak public health systems and private systems that benefit from drug sales.[28] Easy over-the-counter access to antibiotics is a further problem, and it is often difficult to balance improved access to drugs with resistance concerns. A fundamental challenge is that patients, physicians, hospitals, and drug companies have little incentive to consider resistance related costs when deciding how to use, prescribe, or sell antibiotics. But developing countries do not have the luxury of allowing increases in use without taking steps to manage resistance. Reducing the burden of infections through immunisations and hospital infection control could greatly reduce the reliance on antibiotics. Despite strong evidence of benefits, progress on *Haemophilus influenzae* type B and pneumococcal vaccinations has been slow because of economic and other constraints, and no vaccines exist for many other common infections.

Countries could readily adopt steps to accomplish some of these ends while others require long term investment by a range of global players. At present, most evidence of effectiveness for specific interventions comes from high income settings. A challenge, increasingly being taken up, is in adapting interventions to conditions in developing countries, but greater efforts are needed.

Antimicrobial resistance competes with other pressing public health challenges for policy makers' attention. Without sound evidence on the attributable mortality of resistant infections at a national level, it may be difficult to draw resources to this problem, which is urgent but not as obvious as HIV/AIDS or an epidemic of dengue fever, for instance. Similarly, evidence is needed to promote creative solutions that recognise limited regulatory capacities in many low and middle income countries. For instance, a ban on non-prescription sales of antibiotics is likely to be both unenforceable and counterproductive because it may restrict access for poorer populations that rely on private drug sellers for health care. Efforts like the Affordable Medicine Facilities-malaria (AMFm) are promoting the use of coformulations of antimalarials that are less likely to lead to resistance and providing high quality drugs at an affordable price. Similar initiatives could be developed for antibiotics, but they must be accompanied by monitoring for resistance. Ultimately, the way forward will be a combination of many different interventions—better infection control, more appropriate use of antibiotics; research and development of new antibiotics, vaccines, and inexpensive point-of-care diagnostics; less environmental contamination with antibiotics; and stronger surveillance and containment of resistant strains.

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A ban on non-prescription sales of antibiotics is likely to be both unenforceable and counterproductive

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1 Laxminarayan R. Economic issues related to antimicrobial resistance. In: Roberts JA, ed. The economics of infectious disease. Oxford University Press 2006: 49-64.
2 Okeke IN, Laxminarayan R, Bhutta ZA, Duse AG, Jenkins P, O'Brien TF, et al. Antimicrobial resistance in developing countries. Part I: recent trends and current status. *Lancet Infect Dis* 2005;5:481-93.
3 WHO. Community-based surveillance of antimicrobial use and resistance in resource-constrained settings: report on five pilot projects. WHO, 2009.
4 Goossens H, Ferech M, Vander Stichele R, Elseviers M, ESAC Project Group. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005;365:579-87.
5 IMS Health. MIDAS market segmentation data. IMS, 2011.
6 Hamel MJ, Greene C, Chiller T, Ouma P, Polyak C, Otieno K, et al. Does cotrimoxazole prophylaxis for the prevention of HIV-associated opportunistic infections select for resistant pathogens in Kenyan adults? *Am J Trop Med Hyg* 2008;79:320-30.
7 Dong H, Bogg L, Rehnberg C, Diwan V. Health financing policies: Providers' opinions and prescribing behavior in rural China. *Int J Techn Assessm in Hlth Care* 1999;15:686-98.
8 Radyowijati A, Haak H. Improving antibiotic use in low-income countries: an overview of evidence on determinants. *Soc Sci Med* 2003;57:733-44.
9 Sweidan M, Zhang Y, Harvey K, Yang YH, Shen X, Yao K. Proceedings of the 2nd national workshop on rational use of antibiotics in China, Beijing, 28-30 November 2005:1-18. www.docstoc.com/docs/44755790/Proceedings-of-the-2nd-National-Workshop-on-Rational-Use.
10 Dong H, Bogg L, Rehnberg C, Diwan V. Association between health insurance and antibiotics prescribing in four counties in rural China. *Health Policy* 1999;48:29-45.
11 Morgan DJ, Okeke IN, Laxminarayan R, Perencevich EN, Weisenberg S. Non-prescription antimicrobial use worldwide: a systematic review. *Lancet Infect Dis* 2011;11:692-701.
12 Apisarnthanarak A, Tunpornchai J, Tanawitt K, Mundy LM. Nonjudicious dispensing of antibiotics by drug stores in Pratumthani, Thailand. *Infect Control Hosp Epidemiol* 2008;29:572-5.
13 Berkley JA, Mwangi I, Ngetsa CJ, Mwarumba S, Lowe BS, Marsh K, et al. Diagnosis of acute bacterial meningitis in children at a district hospital in sub-Saharan Africa. *Lancet* 2001;357:1753-7.
14 Lim VK, Cheong YM. Bacteriology turnaround time in seven Malaysian general hospitals. *Malays J Pathol* 1992;14:41-3.
15 Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) study. *JAMA* 1995;274:639-44.
16 Vincent J, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009;302:2323-9.
17 Laxminarayan R, Ganguly NK. India's vaccine deficit: why more than half of Indian children are not fully immunized, and what can—and should—be done. *Health Aff* 2011;30:1096-103.
18 Kyaw MH, Lynfield R, Schaffner W, Craig AS, Hadler J, Reingold A, et al. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant Streptococcus pneumoniae. *N Engl J Med* 2006;354:1455-63.
19 Dagan R, Klugman KP. Impact of conjugate pneumococcal vaccines on antibiotic resistance. *Lancet Infect Dis* 2008;8:785-95.
20 Madhi SA, Petersen K, Madhi A, Khoosal M, Klugman KP. Increased disease burden and antibiotic resistance of bacteria causing severe community-acquired lower respiratory tract infections in human immunodeficiency virus type 1-infected children. *Clin Infect Dis* 2000;31:170-6.
21 Jones N, Huebner R, Khoosal M, Crewe-Brown H, Klugman K. The impact of HIV on Streptococcus pneumoniae bacteraemia in a South African population. *AIDS* 1998;12:177-84.
22 Steinfeld H, Chilonda P. Old players, new players. Livestock report 2006. Food and Agriculture Organization of the United Nations, 2006: 3-14.
23 Irungu P, Kariuki S. Analysis of economic incentives influencing farmers' use of antibiotics in livestock production in Kenya. Final report. Center for Disease Dynamics, Economics & Policy, 2011.
24 Joakim Larsson DG, Fick J. Transparency throughout the production chain - a way to reduce pollution from the manufacturing of pharmaceuticals? *Regulatory Toxicol Pharmacol* 2009;53:161-3.
25 Nickerson EK, Hongsuwan M, Limmathurotsakul D, Wuthiekanun V, Shah KR, Srisomang P, et al. Staphylococcus aureus bacteraemia in a tropical setting: patient outcome and impact of antibiotic resistance. *PLoS One* 2009;4:e4308.
26 Trape JF, Pison G, Preziosi MP, Enel C, Desgrées du Loû A, Delaunay V, et al. Impact of chloroquine resistance on malaria mortality. *C R Acad Sci III* 1998;321:689-97.
27 Health Action International. Being sick and needing medicines is a costly misfortune in many countries. 2010. www.haiweb.org/medicineprices/05012010/Global_briefing_note.pdf.
28 Heymann DL. Resistance to anti-infective drugs and the threat to public health. *Cell* 2006;124:671-5.

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