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ANALYSIS

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

Ramanan Laxminarayan *director*[1], David L Heymann *professor and chair*[2]

[1]Center for Disease Dynamics, Economics & Policy, Washington, DC, USA and New Delhi, India; [2]Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

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]

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 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

Correspondence to: D L Heymann david.heymann@hpa.org.uk

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⇓).

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.

Contributors and sources: RL has developed a framework for considering antibiotic effectiveness as a shared global resource and from that perspective has developed policy approaches to improve their use. He directs the Global Antibiotic Resistance Partnership. DLH was executive director of communicable disease at the World Health Organization in 2001 when the global strategy for containment of antimicrobial resistance was developed and oversaw surveillance and response activities of the AMR programme during that period.

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Figures

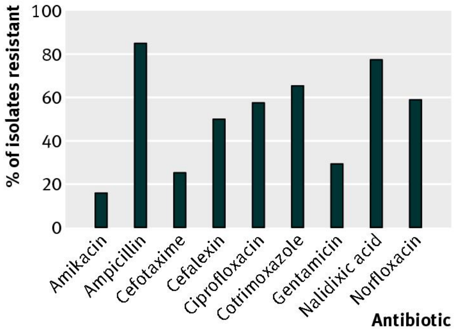

Fig 1 Antibiotic resistance in *E coli* isolated in New Delhi during 2003-4

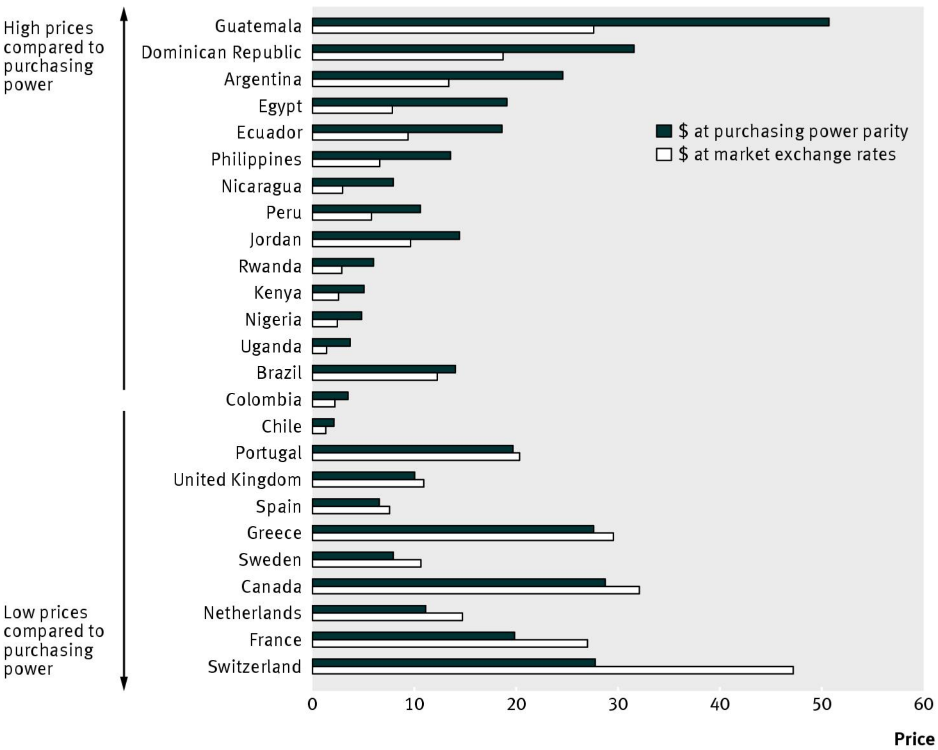

Fig 2 Cost of course of generic ciprofloxacin (500 mg) in selected countries, 30 November 2009[27]