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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

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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, cephalosporins, 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 Escherichia 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 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
Thailand found mortality as high as 67% for meticillin resistant
Staphylococcus aureus and 46% for meticillin susceptible S.
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,
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. 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
coclumulations of antimalarials that are less likely to lead to
resistance and providing high quality drugs at an affordable

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. 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. 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. A study from
Thailand found mortality as high as 67% for meticillin resistant

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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

[Graph showing antibiotic resistance in *E coli* isolated in New Delhi during 2003-4.](#)

[Bar chart showing the cost of a course of generic ciprofloxacin (500 mg) in selected countries, 30 November 2009.](#)