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Antimicrobial resistance in developing countries

C A Hart, S Kariuki

In 1990 it was estimated that 4123 million of the world's 5267 million population—78%—lived in developing countries. Of the 39.5 million deaths in the developing world, 9.2 million were estimated to have been caused by infectious and parasitic disease; infections of the lower respiratory tract were the third most common cause of death worldwide, and diarrhoeal diseases were the fourth.[1] Ninety eight per cent of deaths in children occur in the developing world, mostly as a result of infections.

Projections of disability adjusted life years (that is, the years of life without disability) for the year 2020 show great improvement in developing regions: people are living longer without disabilities.[2] However, even the most pessimistic model analysed did not take into account the possibility that the development of new antimicrobial drugs might slow or cease, and that rates of drug resistance in bacteria such as pneumococci, *Mycobacterium tuberculosis*, or *Staphylococcus aureus* might increase. We chart the progress and impact of bacterial resistance to antimicrobial drugs in the developing world. The information in this review has been assembled from searches of the computerised databases Medline and Bath Information and Data Services, discussions with colleagues, and personal knowledge.

Summary points

- Antibiotics are an important but often scarce resource in developing countries
- Antibiotic use is unregulated in many developing countries; antibiotics are frequently misused and overused
- Resistance to antimicrobial drugs is causing increasing mortality and morbidity from infectious diseases
- Particular problems of resistance are seen in pneumococcal meningitis, tuberculosis, and typhoid fever
- To maintain the useful life of antimicrobial drugs in developing countries there needs to be improved access to diagnostic laboratories, improved surveillance of the emergence of resistance, better regulation of the use of antibiotics, and better education of the public, doctors, and veterinarians in the appropriate use of the drugs

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Availability of antimicrobial drugs

Although even the most potent and recently developed antimicrobial drugs are available throughout the world, in developing countries their use is confined to those who are wealthy enough to afford them. In tertiary referral hospitals such as the Kenyatta National Hospital in Nairobi, Kenya, the first line antimicrobial drugs used are ampicillin, chloramphenicol, co-amoxiclav, co-trimoxazole, erythromycin, gentamicin, penicillin, and tetracycline. Amikacin, cefuroxime, ciprofloxacin, and nalidixic acid are used as second line agents. In district hospitals only the first line agents are available, but sometimes not even these are available.

Ducklings in the Thika district, Kenya, have continuous access to drinking water that is heavily laced with tetracycline

In 1988 it was estimated that the cost of providing drugs for treating sexually transmitted infections occurring in 1 million people per year in Mozambique was $137 587 (£85 881) or $0.13 (8 pence) per person (table 1).[3] However, even this comparatively small sum is beyond the means of some developing countries. Additionally, the calculations did not take account of the possibility of the emergence of gonococci resistant to kanamycin, spectinomycin, or tetracycline. Nor was the resistance of *Haemophilus ducreyi* to erythromycin or co-trimoxazole, or the resistance of *Calymmatobacterium granulomatis* to co-trimoxazole, considered.

How are antimicrobial drugs used?

In many developing countries the use of antimicrobial drugs for treating people and animals is unregulated; antibiotics can be purchased in pharmacies, general stores, and even market stalls. In the Rajbari district of Bangladesh, a survey of rural medical practitioners (barefoot doctors) with an average of 11 years' experience showed that they each saw on average 380 patients per month and prescribed antibiotics to 60% of these patients on the basis of symptoms alone.[4] In one month 14 950 patients were prescribed antibiotics—a total of 291 500 doses. Only 109 500 doses had been dispensed by pharmacies, and a further 100 000 doses had been dispensed without a prescription.[4]

Table 1 Cost of drugs to treat sexually transmitted infections per million population in Mozambique, 1988. Reprinted with permission[3]

Drug and dose (delivery)	Unit price ($)	Units used/ 1 000 000 population	Cost ($)
Benzathine penicillin 2.4 MU (intramuscular)	0.35	41 275	14 446
Kanamycin 2 g (intramuscular)	0.62	122 500	75 950
Spectinomycin 2 g (intramuscular)	1.61	6 250	10 063
Erythromycin 500 mg (oral)	0.077	82 500	6 353
Erythromycin syrup (oral)	0.56	2 500	1 400
Metronidazole 250 mg (oral)	0.0065	500 000	3 250
Co-trimoxazole 80:400 mg (oral)	0.015	427 000	6 405
Nystatin pessary (vaginal)	0.02	42 000	840
Crystal violet 250 g pack (topical)	6.50	40	260
Tetracycline eye ointment (topical)	0.5	10 000	5 000
Total		1 234 065	137 587

Thus there is widespread and uncontrolled use of antibiotics, and patients often do not take a full course of treatment if they are unable to afford it. Another problem in developing countries is the quality and potency of antimicrobial drugs. In some countries many different antimicrobial drugs are produced locally. In India, for example, there are over 80 different brands of the fluoroquinolone ciprofloxacin. In Vietnam a locally acquired 500 mg capsule of ciprofloxacin costs 400 dong (about 2 pence). The average weight of the capsules is 405 mg with a potency equivalent to 20 mg of pure ciprofloxacin (J Wain, personal communication).

Enteric pathogens

Diarrhoeal disease is a major cause of morbidity and mortality in developing countries. Although rotavirus infections are an important cause of the disease in infants,[5] bacteria are the most important pathogens in older children and adults. Because laboratory facilities are not widely available most patients are treated empirically and usually with antibiotics. Infection with *Shigella* spp and *Vibrio cholerae* frequently causes epidemics. Over the years *Shigella* spp have shown a great propensity to develop resistance to antibiotics. For example, in 1996 in Matlab and Dhaka, Bangladesh, over 95% of *Shigella dysenteriae* isolates were resistant to ampicillin, co-trimoxazole, and nalidixic acid, and 14-40% were resistant to mecillinam.[6] This was a large increase over the 1% of resistant isolates identified in 1991, before the drug was widely available. During cholera epidemics the bacterium has the ability to develop increasing resistance, usually by acquisition of plasmids. In Somalia in a cholera epidemic in 1985-6 there was a case fatality rate of 13% because the initially sensitive *V cholerae* quickly acquired plasmid encoded resistance to ampicillin, kanamycin, streptomycin, sulphonamides, and tetracycline.[7]

Respiratory tract infections

Acute respiratory tract infections cause 3.5 million deaths in children each year.[8] The most important pathogens associated with pneumonia are *Haemophilus influenzae* and *Streptococcus pneumoniae*. Penicillin resistant pneumococci were first reported in Australia and New Guinea in the 1960s, and until recently their biggest impact had been in developing countries.[9] Resistance is characterised as intermediate (minimum inhibitory concentration 0.12 mg/l to 1.0 mg/l) or high (< 1.0 mg/l) and is due to alterations in penicillin binding proteins which have a much lower affinity for penicillin.

Pneumococci highly resistant to penicillin first emerged in South Africa in 1977.[10] The prevalence of penicillin resistant pneumococci in infection and carriage sites varies but seems to be increasing. However, there are large gaps in our knowledge of the prevalence of resistance worldwide (table 2).[11–14] Multidrug resistant pneumococci and pneumococci resistant to penicillin have spread globally; the serotype 23F clone, for example, which probably originated in Spain has also been found in Mexico, South Africa, South Korea, Portugal, Croatia, France, and the United States.[15] Many penicillin resistant pneumococci are also resistant to chloramphenicol. Highly resistant pneu-

mococci may also be resistant to cephalosporins such as cefuroxime and ceftriaxone, thus limiting treatment options.

M tuberculosis has always been active in developing countries. The AIDS epidemic has increased the impact of tuberculosis and may have led to a gradual increase in resistance to antituberculous drugs. In a recent global survey 9.9% of *M tuberculosis* isolates from previously untreated patients were resistant to one of the first line drugs (rifampicin, streptomycin, isoniazid, or ethambutol).[16] Areas that had the greatest prevalence of resistance to one drug among previously untreated patients were the Dominican Republic (26% of isolates), Thailand (21.4% of isolates), Vietnam (19% of isolates), and Sierra Leone (17% of isolates).[16] Worldwide 0.2% of *M tuberculosis* isolates were resistant to all four first line drugs but the highest prevalence of resistance was in the former Soviet Union.

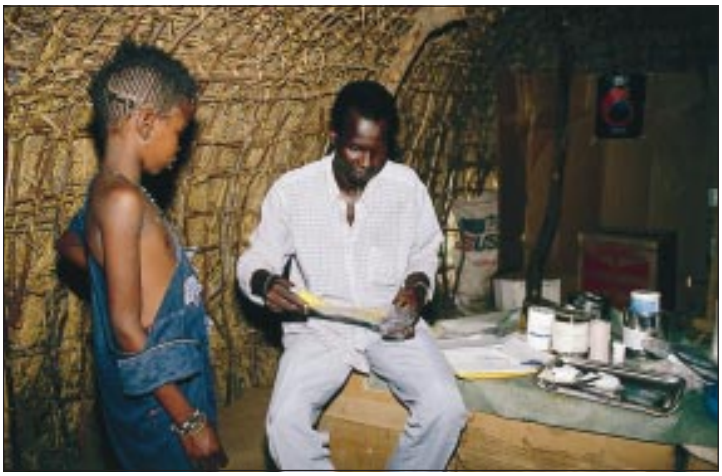
Meningitis

Except in sub-Saharan Africa where meningococcal meningitis is endemic and epidemic *S pneumoniae* is the major cause of bacterial meningitis.[17] There are numerous reports of the failure of penicillin treatment in meningitis (because of the existence of both intermediate and highly resistant pneumococci); thus the use of penicillin as an empirical treatment for meningitis in tropical countries is endangered. Cefotaxime is an alternative but resistance to this and chloramphenicol is not uncommon. This leaves glycopeptides such as vancomycin, used with or without rifampicin, as the only alternatives.[18]

Infection with *Neisseria meningitidis* causes large outbreaks of meningitis in sub-Saharan Africa.[19]

Table 2 Prevalence of penicillin resistant pneumococci (PRP) in the developing world[11-14]

Country	Year	No of PRP isolated/total pneumococci identified (%)
Clinical isolates		
Africa:		
Kenya	1975-9	15/151 (10)
Malawi	1995	2/9 (22)
Rwanda	1984-90	80/383 (21)
South Africa	1983-5	249/3568 (7)
	1990	156/1100 (14.2)
Asia:		
Bangladesh	1989-91	6/51 (12)
Pakistan	1986-9	8/87 (9)
	1989-90	9/81 (11)
South America:		
Brazil	1989-90	25/150 (17)
Chile	1983-5	39/178 (22)
Carriage isolates		
Africa:		
Malawi	1995	12/52 (23)
Nigeria	1978	1/50 (2)
South Africa	1977	168/270 (62)
	1981	21/178 (12)
	1985	73/302 (24)
	1985	26/113 (23)
Zambia	1986	1/39 (3)
Asia:		
Pakistan	1989-90	
Urban areas		7/49 (14)
Rural areas		9/132 (7)



JEREMY HARTLEY/PANOS PICTURES

In many developing countries antibiotics can be purchased over the counter in pharmacies, general stores, and market stalls

Penicillin resistant meningococci have emerged in Africa: 8% of meningococci isolated in the 1986-92 epidemic in Malawi showed intermediate resistance to penicillin.[19 20]

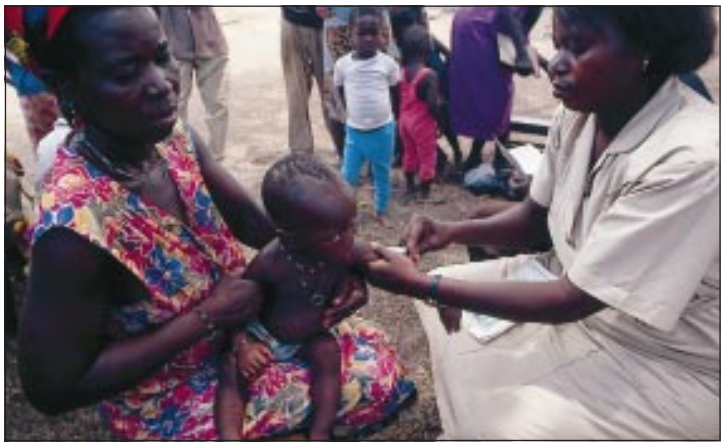
Sexually transmitted infections

Sexually transmitted infections are among the most frequently occurring infections worldwide. It has been estimated that among adults aged 15-49 there were 332 million cases of sexually transmitted infections worldwide. Syphilis accounted for 3.6% of the total number of cases, gonorrhoea for 18.7%, chlamydiosis for 26.6%, and trichomoniasis for 51.1%; over 76% of these infections occurred in the developing world.[21] *Neisseria gonorrhoeae* has shown great versatility in developing resistance to antimicrobial drugs including sulphonamides, penicillins, and tetracycline. Fluoroquinolones such as ciprofloxacin and ofloxacin have proved highly effective in treating gonorrhoea but after widespread and often inappropriate use fluoroquinolone resistant *N gonorrhoeae* has emerged.[22] In some areas this leaves third generation cephalosporins, such as cefotaxime or ceftriaxone, as the only predictably effective antibiotic treatment for gonorrhoea.

Disseminated infections

Typhoid is endemic in the developing world; an estimated 16 million cases occur each year resulting in some 700 000 deaths. Mortality has been greatly reduced through the use of antimicrobial drugs; chloramphenicol, ampicillin, or co-trimoxazole are the first line drugs used. Unfortunately, multidrug resistant *Salmonella typhi* emerged in 1987 and has spread throughout the Indian subcontinent and South East Asia.[23] These isolates carry large, self transmissible plasmids which can encode resistance to each of the first line drugs; in Quetta, Pakistan, for example, 69% of *S typhi* isolated from blood were multidrug resistant.[23] Fluoroquinolones have become the first line drugs for such infections but resistance has emerged and this has led to failures in treatment.[24] There is currently an epidemic of infection associated with ciprofloxacin resistant *S typhi* in Tajikistan.[25]

Plague is a re-emerging zoonosis caused by *Yersinia pestis*. Infection is usually treated with streptomycin, chloramphenicol, tetracycline, or gentamicin. In a recent



LIBA TAYLOR/PANOS PICTURES

Empirical management strategies can lead to overtreatment

epidemic in Madagascar, a strain of *Y pestis* emerged that was resistant to ampicillin, chloramphenicol, streptomycin, spectinomycin, kanamycin, tetracycline, and sulphonamides; resistance was encoded on a large, self transmissible plasmid.[26] If this resistance becomes established it could render plague untreatable.

Nosocomial infections

Bacteria resistant to treatment with antibiotics are undoubtedly spread in hospitals in developing countries. Resistant primary pathogens (for example, *S typhi, S pneumoniae,* and *M tuberculosis*) and hospital acquired bacteria (*Klebsiella pneumoniae*, *Escherichia coli*, and *Pseudomonas aeruginosa*) do cause problems. Methicillin resistant *S aureus* (MRSA) is a growing problem in many parts of the developing world including Kenya,[27] Sri Lanka,[28] and Tunisia.[29] The most important factors associated with its spread were found to be poor hospital hygiene, overcrowding, lack of resources for infection control, and a lack of personnel trained in controlling infections in hospital.[27–29]

Conclusion

We do not wish to give the impression that developing countries are awash with bacteria that are resistant to antibiotics. Many bacteria (for example, *Chlamydia trachomatis* and *Streptococcus pyogenes*) remain predictably sensitive to routinely available antimicrobial drugs. However, we do not wish to encourage complacency. Antibiotic resistant bacteria are associated with the failure of treatment and increased mortality and morbidity.

Antimicrobial drugs are an important resource that must be conserved for future use. To do this requires knowledge of the size of the problem and early warnings of the emergence of resistant isolates. In developing countries laboratory diagnostic facilities are scarce and this has led to the introduction of empiric, pragmatic, and problem oriented management strategies for the administration of antimicrobial drugs. Inevitably this results in overtreatment.

For the future the priority must be to improve the laboratory infrastructure in developing countries. This will not only benefit individual patients but will also provide early warnings of the emergence of resistant isolates and surveillance data on trends. This will be expensive but the cost must be balanced against the risk of the development of untreatable infections in vulnerable populations. Finally, there must also be greater regulation of the use of antibiotics in developing countries; this must be accompanied by strategies to educate the public, doctors, and veterinarians on the appropriate use of antibiotics.

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