Socioeconomic and Behavioral Factors Leading to Acquired Bacterial Resistance to Antibiotics in Developing Countries

Iruka N. Okeke,* Adebayo Lamikanra,* and Robert Edelman†
*Obafemi Awolowo University, Ile-Ife, Nigeria; and †University of Maryland School of Medicine, Baltimore, Maryland, USA

In developing countries, acquired bacterial resistance to antimicrobial agents is common in isolates from healthy persons and from persons with community-acquired infections. Complex socioeconomic and behavioral factors associated with antibiotic resistance, particularly regarding diarrheal and respiratory pathogens, in developing tropical countries, include misuse of antibiotics by health professionals, unskilled practitioners, and laypersons; poor drug quality; unhygienic conditions accounting for spread of resistant bacteria; and inadequate surveillance.

Acquired bacterial resistance is common in isolates from healthy persons and from patients with community-acquired infections in developing countries, where the need for antibiotics is driven by the high incidence of infectious disease (1). Among isolates of diarrheal, respiratory, and commensal enteric pathogens (2-5), resistance is increasing, particularly to first-line, inexpensive, broad-spectrum antibiotics (Table 1). Furthermore, introduction of newer drugs (e.g., fluoroquinolones) has been followed relatively quickly by the emergence and dissemination of resistant strains (5). The selection and spread of resistant organisms in developing countries, which can often be traced to complex socioeconomic and behavioral antecedents, contribute to the escalating problem of antibiotic resistance worldwide.

Table 1. Pathogens with a steadily increasing prevalence of acquired antibiotic resistance in developing tropical countries

Pathogen	Drug(s)	Country (years)	Ref.
Shigella flexneri, *S. dysenteriae*	ampicillin, tetracycline, sulfonamides (alone or with trimethoprim), nalidixic acid	Bangladesh (1983-1990)	(6)
		Brazil (1988-1993)	(7)
		Rwanda (1983-1993)	(8)
		Thailand (1981-1995)	(5)
Vibrio cholerae	cotrimethoxazole, nalidixic acid, ampicillin	Guinea-Bissau (1987-1995)	(9)
		India (1993-1995)	(10)
Salmonella typhi	ampicillin, chloramphenicol, cotrimethoxazole	Bangladesh (1989-1993)	(3)
Salmonella (nontyphoidal)	cotrimethoxazole	Thailand (1981-1995)	(5)
Enterotoxigenic *Escherichia coli*	cotrimethoxazole	Thailand (1981-1995)	(5)
Campylobacter	fluoroquinolones	Thailand (1987-1995)	(5)
Mycobacterium tuberculosis	isoniazid, streptomycin, rifampicin (primary resistance)	Kenya (1981-1990)	(11)
		Morocco (1992-1994)	(12)

Address for correspondence: Robert Edelman, Center for Vaccine Development, 685 West Baltimore St., Room 480, Baltimore, MD 21201, USA; fax: 410-706-6205; e-mail: redelman@umppa1.ab.umd.edu.

Misuse of Antibiotics by Physicians in Clinical Practice

Antibiotic use provides selective pressure favoring resistant bacterial strains; inappropriate use increases the risk for selection and dissemination of antibiotic-resistant bacteria, which are placed at a competitive advantage. Therefore, one would expect that drugs more commonly affected by bacterial resistance in developing countries are generally inexpensive and popular broad-spectrum agents (2-5,13). However, the relationship between antibiotic use and the emergence and spread of resistance is complex. Antibiotic use in clinical practice alone cannot explain the high frequency of resistant organisms in developing countries (14,15). Nevertheless, excessive clinical use (a form of misuse) is at least partially responsible for the escalating rates of resistance, especially in hospital settings, worldwide. The unnecessary prescription of antibiotics seen in industrialized nations has also been documented in many developing countries, particularly in cases of acute infantile diarrhea and viral respiratory infections (16-22). Clinical misuse of antibiotics may be more common among private practitioners than among public health personnel—private practitioners charge higher fees, the demand for antibiotics seen in private patients is higher, and more drugs are available in private clinics than in public hospitals (23-25).

Several strategies have been proposed for combating the inappropriate use of antibiotics by clinicians (26). Antibiotic monitoring systems and hospital formularies or antibiotic treatment protocols often reduce antibiotic prescription rates (24,27). Adoption of a national essential drug list can limit the antibiotics available to prescribers (28,29). However, implementation of these strategies does not guarantee optimal antibiotic use by clinicians in developing countries because the irregular drug supply, availability of drugs from unofficial sources, and financial constraints also affect antibiotic choices (30-32).

Continuing medical education changes the attitude of clinicians. Studies of antibiotic misuse in Cuba and Pakistan (33,34) recommend continuing medical education for health workers as the single most important tool for combating antibiotic misuse. A study in Zambia has demonstrated the efficacy of education in reducing antibiotic prescription rates (35). However, education has not been successfully implemented in many developing countries, where too often, governments and health workers cannot afford the time and money required for continuing medical education (36).

Health workers in many developing countries have almost no access to objective health information (24). Pharmaceutical company representatives typically outnumber practitioners and often adversely influence their prescription habits (37), as reflected by sales of nonessential drugs and drug combinations (38). Drug labels and package inserts often fail to provide accurate information (39), and in industrialized countries, patients often pressure physicians to prescribe antibiotics (19).

Misuse of Antibiotics by Unskilled Practitioners

In many developing countries, well-trained health personnel are scarce and cannot serve the entire population, especially in rural areas. Community health workers and others with minimal training treat minor ailments (40). The qualifications and training of community health workers, as well as the quality of care they provide, vary from country to country. Unskilled personnel are less aware of the deleterious effects of inappropriate antibiotic use. For example, pharmacy technicians in Thailand prescribed rifampicin for urethritis and tetracycline for young children (41). Unqualified drug sellers offer alternative drugs when the prescribed drugs are out of stock or refill prescriptions without consulting the prescriber (42,43). In India, traditional healers often dispense antibiotics (44). A high proportion of patients in some developing countries are treated by untrained practitioners simultaneously with oral and injectable antibiotics administered with contaminated needles and syringes (45-47) for misdiagnosed noninfectious diseases (48).

Misuse of Antibiotics by the Public

In most developing countries, antibiotics can be purchased without prescription, even when the practice is not legal. In many African, Asian, and Latin American countries, antibiotics are readily available on demand from hospitals, pharmacies, patent medicine stalls (drugstores), roadside stalls, and hawkers (17,43,46,49-53). In rural Bangladesh, for example, 95% of drugs consumed for 1 month by more than 2,000 study participants came from local pharmacies; only

8% were prescribed by physicians (54). People are encouraged to buy from unofficial distributors because drugs often are not available in government hospitals (55). Drug vendors usually have little or no knowledge of the required dosage regimen, indications, or contraindications (43,45,55). In markets and public transport in West African countries such as Cameroon (49) and Nigeria (Okeke and Lamikanra, pers. obs.), the vendor (usually a medically untrained salesman) tries to convince potential buyers to purchase the drug, even if they are not ill.

To save time and keep drug-hunting to a minimum, a patient may start at a source more likely to stock the desired drug, forgoing the expertise of a doctor. Unofficial sources are generally more accessible than official sources. For example, in Nepal, retail drug outlets are four times as numerous as government health posts and hospitals (46). Alternate sources offer the option of purchasing small quantities of medicines, while hospitals require purchase of the complete 5- or 7-day antibiotic regimen (17,43,52). The purchase of small samples is exceedingly common, particularly for most customers, who buy without prescription (52). These subinhibitory antibiotic regimens predispose for selection of resistant bacterial strains.

Antibiotic use in developing countries is underestimated. The quantity of drugs distributed within a country is calculated under the assumption that each person purchases a complete regimen (56). However, medication can be purchased in small aliquots from roadside stalls, and distribution of locally produced or counterfeit antibiotics is not recorded. The motives for self-medication and antibiotic overuse by laypersons are similar to those for clinical abuse by health professionals: to cut costs and act expeditiously to treat confirmed or suspected bacterial infection (57). For example, 50% to 80% of Bangladeshi patients infected with *Shigella* admitted that they had taken at least one antibiotic in the 15 days before a hospital visit (58), as had 18% to 70% of pediatric patients with acute respiratory infection in two Chinese studies (20,59). The proportion of patients who self-medicate is probably higher, because patients are often reluctant to admit having taken antibiotics before visiting a hospital (60).

Common cultural beliefs about antibiotics include the notions that there is a pill for every symptom; antibiotics can heal many illnesses, including dyspepsia and headaches; and injections are more powerful than pills. The misuse of antibiotics frequently becomes integrated into the local culture (62) (e.g., antibiotics are used to prevent diarrhea after eating suspected contaminated foods or [by prostitutes] to prevent sexually transmitted diseases [52,63]).

Another cause of antibiotic abuse and selection for resistant bacteria is poor patient compliance. First, physician-patient interactions are often inadequate. They can be short (e.g., a mean of 54 sec was recorded in a Bangladeshi study [16]) and of poor quality (e.g., in Mexico, poor patient-physician communication was partially responsible for the noncompliance of patients with antibiotic regimens [21]). Second, because patients often travel long distances and incur large expenses for medical care, they are unlikely to return for follow-up visits. The reverse situation—the prescriber visiting his patient—is difficult logistically, especially in rural Africa (64). In addition, the patient may be unable to read medicine labels. Finally, because many drugs are expensive, indigent patients purchase incomplete regimens whenever possible and discontinue treatment when symptoms disappear but before the pathogen is eliminated (52).

Poor Quality of Antibiotics

Lack of Quality Compliance and Monitoring

Besides the risk for therapeutic failure, degradation products or adulterants in poor quality antibiotics can produce subinhibitory concentrations in vivo, which increase the selection of resistant strains. Drugs that do not comply with minimum standards are illegal in all countries. However, the quality of many antibiotics and other drugs in developing countries is often below standards in the formulary. In Nigeria for example, substandard ampicillin, ampicillin/cloxacillin, tetracycline, and oxytetracycline capsules have been detected (53,65-67). In many cases, therapeutic failure is the only indication of substandard drugs. Analytic laboratories to detect substandard drugs are uncommon, and when they exist, health workers, distributors, and consumers are often unaware of them.

Degraded Antibiotics

The shelf lives of drugs developed and marketed in temperate countries are determined by storage temperatures. During distribution in tropical countries, conditions of transport and storage are poorly controlled, and the drugs may be degraded. Ballereau et al. (68) recorded temperatures of 26°C to 40°C and 30% and 90% humidity in Guinea-Bissau during a 2-year period (temperatures of greater than 25°C can degrade antibiotics). Many antibiotics, being heat- and moisture-labile, are particularly vulnerable. Of seven drugs that lost 10% or more of their active constituents when stored in pharmacies in Guinea-Bissau for 2 years, six were antimicrobial drugs (68). Drug consignments are exposed to such adverse conditions during shipment (69) or at tropical ports while they await lengthy port clearance. Drugs are often handled by untrained workers who may store them incorrectly. Hawkers and small traders in Nigeria frequently display large glass jars containing different types of antibiotic capsules mixed together, fully exposed to harsh sunlight and high ambient temperature and humidity. In a Nigerian study of eight batches of tetracycline capsules, only the batch obtained directly from the manufacturer was not excessively degraded and contained active drug levels within formulary limits (Table 2) (53,70). Studies conducted in Thailand and Nigeria demonstrated similar degradation of chloroquine and amoxicillin (67,70).

Table 2. Source and quality of tetracycline capsules in a Nigerian suburban town (compiled with data from [53])

Sample	Source	Tetracycline content (% of label claim)	Content of ATC[a] (%)	Bioavailability (%)[b]
C1	Manufacturer[c]	105.9	None detected	100
C2	Hospital	107.5	5.3	63.4[d]
C3	Roadside stall	104.5	1.1	80.5[d]
C4	Pharmacy	66.1	2.4	65.2[d]
C5	Patent medicine stall	84.5	1.9	87.6[d]
C6	Roadside stall	67.8	1.5	Not tested
C7	Patent medicine stall	89.6	1.8	Not tested

[a]Anhydrotetracycline, one of four tetracycline degradation products.
[b]Measured from cumulative excretion of tetracycline in the urine of five volunteers.
[c]Reference standard obtained from the manufacturer.
[d]Significantly different from C1 ($p = 0.01$, Wilcoxon signed rank test).

Expired Antibiotics

Some pharmacologically active drugs produced in industrialized countries have expired when distributed in developing countries—they were shipped at the end of the drugs' shelf lives or their clearance and distribution after transcontinental shipment were delayed. Expired drugs may receive new labels, be dumped without a label change, or be donated rather than sold (71-73). Tax deductions and the cost of liquidation are incentives for donating expired or near-expired drugs. Effective enforcement of the World Health Organization (WHO) guidelines on drug donations may curtail such practices (74).

Counterfeit Drugs

Some drugs sold in developing countries do not contain the concentration of active substances stated on their labels, even at the time of manufacture. These counterfeit drugs flourish, despite efforts of local regulatory agencies to stop their production and distribution (75-77). Approximately 65% of the 751 instances of counterfeit pharmaceuticals reported to WHO or to Interpol from 28 countries in the past 15 years were produced in developing countries (77). Counterfeit drugs include products with little or no active ingredients (e.g., in Nigeria, Indonesia, Brazil, Thailand, Bangladesh, Malaysia, and Francophone African countries [39,76,78,79]) or products for which excipients have been replaced by less expensive alternatives (e.g., substitution of ethylene glycol for propylene glycol in pediatric paracetamol formulations, which caused many deaths in Nigeria, Argentina, Bangladesh, India, and Haiti [76,78]). Counterfeit drugs, like other counterfeit materials, compete favorably in the markets of developing countries. The analytic facilities available to law enforcement agencies often cannot detect these drugs before they reach the patient. Multinational pharmaceutical companies, which probably possess the best analytic facilities for in-house quality assurance in developing countries, try to detect counterfeit drugs to protect their income and reputation; however, such efforts are directed primarily at counterfeits of these companies' own products. Because of the profusion of generic drugs in developing countries, a substantial proportion of counterfeit drugs go undetected.

Adulterated Drugs

Herbal preparations in developing countries are often adulterated with orthodox medicaments. For example, in one study, 24% of Chinese herbal preparations marketed in Taiwan contained one or more of such adulterants (80). Although the adulteration of such products with antibiotics has not been reported, such practices may be common (81). A Nigerian traditional healer, for example, admitted to 'augmenting' herbal preparations with tetracycline from commercially available capsules (82).

Bioinequivalent Antibiotics and Biopharmaceutic Interactions

In the last 2 decades, the importance of bioavailability has been underscored by the recognition that chemically equivalent generic drug formulations do not always deliver the expected amount of drug to the bloodstream. Slowly absorbed and acid-labile antibiotics are particularly prone to bioinequivalence and consequent therapeutic failure. In addition, poorly absorbed antibiotics remain in the gut to facilitate the selection of resistant organisms. The few published studies from the developing world have found bioinequivalence in antibiotic formulations, and the problem may be widespread (Table 2) (53,83). Inexpensive generic antibiotics commonly used in developing countries usually are not subject to bioavailability studies.

The bioavailability of an antibiotic formulation is modulated by conditions surrounding its administration; conditions unique to developing countries are rarely investigated. Drug combinations used in the tropics but rarely elsewhere may not be optimally absorbed. For example, coadministration of chloroquine and ampicillin lowers the bioavailability of ampicillin (84). A Nigerian meal lowered the biologic availability of orally administered nitrofurantoin (85). Chewing of Khat, a popular Yemeni stimulant, adversely affected the bioavailability of ampicillin and amoxicillin (86). By contrast, the Ayurvedic preparation Trikatu enhanced the absorption of several drugs (87). Whether traditional medicines with antimicrobial properties enhance antibiotic resistance is unknown.

Dissemination of Resistant Organisms

Crowding and Unhygienic Conditions

Residents of developing countries often carry antibiotic-resistant fecal commensal organisms (13,88). Visitors to developing countries passively acquire antibiotic-resistant gut *Escherichia coli,* even if they are not taking prophylactic antibiotics, which suggests that they encounter a reservoir of antibiotic-resistant strains during travel (89). Apparently healthy people in developing countries carry potentially pathogenic, antibiotic-resistant organisms asymptomatically (90). Several factors, such as urban migration with crowding and improper sewage disposal, encourage the exchange of antibiotic-resistant organisms between people and the exchange of resistance genes among bacteria, thereby increasing the prevalence of resistant strains. In Nigeria, resistant *E. coli* isolates from persons in an urban metropolis (Lagos) were significantly more likely to be resistant to ampicillin and streptomycin ($p \leq 0.05$), and possibly more resistant to sulphathiazole and tetracycline ($p \leq 0.10$), than isolates from residents of nearby smaller towns and villages (Table 3) (91). Moreover, strains isolated from Lagos were more likely to show resistance to 4 to 6 of 7 antibiotics tested, whereas strains from rural areas were in most cases resistant to only 0 to 3 antibiotics (91).

In 1991, 80% of residents of developing countries had no sanitary facilities for sewage disposal (92). Pipe-borne water, often scarce in developing countries, is not always potable. The

Table 3. Antibiotic resistance of *Escherichia coli* strains isolated from residents of an urban area (Lagos) or rural/suburban areas (southwest Nigeria) (from [91])

Antimicrobial agent	Percentage of resistant isolates: Urban (n = 30)	Rural/suburban (n = 44)
Ampicillin[a]	53	27
Chloramphenicol	13	14
Streptomycin[a]	63	32
Sulphathiazole[b]	73	48
Tetracycline[b]	87	64
Trimethoprim	53	41

[a]Significant differences between the two groups at $p \leq 0.05$ (Chi-square test)
[b]Significant differences between the two groups at $p \leq 0.10$ (Chi-square test)

development of sanitation and other facilities is not always proportionate to the rapid rises in urban populations (93,94). As urban migration continues, overcrowding increases and hygiene declines, increasing the probability of spread of antibiotic-resistant and commensal pathogens. Potable water, well-ventilated housing and proper waste disposal should reduce infections, the need for antibiotics, and subsequent development of antibiotic resistance.

Because tropical conditions encourages the survival of bacteria, more pathogens and commensals are found in tropical environments than in temperate climates (95). The warm and humid tropical climate and the low levels of health care, hygiene, and sanitation contribute to a relatively high prevalence of infectious disease in developing countries.

Inadequate Hospital Infection Control Practices

Infection control practices in many hospitals in developing countries are rudimentary and often compromised by economic shortfalls and opposing traditional values (96). The resulting nidus of nosocomial pathogens and resistant organisms may be disseminated to the outside community. Improper disposal of hospital waste accentuates such spread. Untreated hospital waste in Uganda was often dumped into public sewers or thrown into rubbish heaps ravaged by scavengers (97).

Inadequate Surveillance

Susceptibility Testing and Surveillance

Information from routine susceptibility testing of bacterial isolates and surveillance of antibiotic resistance, which provides information on resistance trends, including emerging antibiotic resistance, is essential for clinical practice and for rational policies against antibiotic resistance. Bacterial infections are often treated after they become life-threatening, which encourages empirical selection of broad-spectrum antibiotics (98,99). The antibiotic susceptibility pattern of bacterial isolates in much of the developing world is unknown, and little guides empirical prescribing. Susceptibility testing cannot be done readily because equipment, personnel, and consumables are scarce and expensive (59,100). In most all infections, no clinical specimens are cultured. Where available, community-based antibiotic surveillance data may be useful to prescribers in the absence of patient-specific antibiotic-susceptibility results. For example, Ringertz et al. (101) demonstrated that resistance among respiratory pathogens was infrequent in parts of Ethiopia. This information would help local Ethiopian prescribers to treat such infections with inexpensive, broad-spectrum antibiotics.

National surveillance programs for antibiotic resistance, the norm in industrialized nations, are less common and less elaborate in developing countries (4). Current inferences about antibiotic resistance trends in developing countries are based on a small number of reports, generated by a handful of microbiology laboratories in urban areas—data not representative of a country, because wide variations in antibiotic resistance patterns may exist within countries (Table 3). Moreover, surveillance should be conducted regularly and continuously because resistance rates can vary in one region of a country over time (Table 1) (102).

Defective Antibiotic Susceptibility Assays

Well-standardized antibiotic susceptibility assays provide more reliable results (103). However, standard bacterial strains with which to assay new batches of antibiotics or antibiotic disks are not available in laboratories in many developing countries. Delayed transportation and breakdown of cold storage also affects the quality of antibiotics used as diagnostic reagents. Degraded antibiotic powders and antibiotic disks used for susceptibility testing lead to exaggerated estimates of bacterial resistance levels. The frequent recovery of bacteria resistant to the beta-lactams or tetracyclines in tropical countries could reflect, in part, the temperature and moisture lability of test reagents. Laboratory scientists in developing countries face difficulties in obtaining research supplies, which often require them to improvise by, for example, using injectable antibiotic formulations to measure MICs when standard antibiotic powders are not available. The report that clinical microbiologists in developing countries make their own disks from "local blotting papers" (104) illustrates how improvisation can lead to inconsistent laboratory results and unreliable data.

Economic and Political Factors

Lack of resources hampers implementation of most strategies against antibiotic resistance. Statistics from the World Bank show that developing countries spent $41 per person on health in 1990, compared with the $1,500 per person spent by industrialized countries. Disease prevalence as measured by disability-adjusted life years and by communicable disease in particular is much greater in developing than in industrialized countries (93,105-107). As a result of such gross underfunding, the drug supply is chronically inadequate or at best erratic in health facilities in many countries, including Nigeria (43,105,106).

Armed conflicts have recently led to a breakdown in health services and sanitation and rapid dissemination of resistant pathogens, particularly in sub-Saharan Africa and Asia (108,109,110). During an outbreak of cholera and bacillary dysentery in Rwandan refugees, resistance to multiple first-line antibiotics in clinical isolates of *Vibrio cholerae* and *Shigella dysenteriae* contributed to high death rates (109).

Even in developing countries not at war, political corruption and mismanagement of funds, personnel, and development programs have created large populations living in abject poverty and at high risk for infection (111). Medical expenses, days lost from work, and transportation costs account for substantial economic loss. The cost of medical treatment, even subsidized treatment, is beyond the means of many patients. Poorly paid health workers sometimes extort fees from patients (111). Thus, persons with communicable diseases, unable to afford medical treatment, may infect others. Poverty also interferes with patient compliance, which in turn promotes the emergence of antibiotic resistance during short-term therapy of acute infections and long-term therapy of chronic infections, such as tuberculosis (111).

Combating the Problem of Antibiotic Resistance

The recommendations of WHO for ensuring proper drug use (79) can be adapted to combat the escalation of community-acquired antibiotic resistance in developing countries. The misuse of antibiotics by health-care professionals, unskilled practitioners, and patients can be alleviated by auditing antibiotics, limiting antibiotic choice, developing prescription guidelines, and emphasizing continuing medical and public education. The quality of antibiotics can be improved by emphasizing quality compliance and monitoring antimicrobial drugs manufactured or dispensed. Such reforms will help control substandard drugs that are degraded, counterfeit, or bioinequivalent. Dissemination of resistant organisms in the community can be impeded by improved public sanitation and hygienic practices and upgraded hospital infection control. Finally, strategies to ensure that these recommendations are adopted and implemented under difficult economic and political conditions can be formulated. Antimicrobial resistance will continue to escalate in developing countries unless corrective measures are instituted.

Acknowledgments

We thank the International Program in the Chemical Sciences, which supports the current research in antibiotic resistance by I.N. Okeke and A. Lamikanra. Ms. I.N. Okeke thanks the Fulbright Commission and the United States Information Service for a fellowship and Dr. James B. Kaper for his support.

Ms. Okeke, lecturer in pharmaceutical microbiology at Obafemi Awolowo University, Ile-Ife, Nigeria, and Ph.D. candidate, is a Fulbright Fellow at the Center for Vaccine Development in Dr. James Kaper's laboratory at the University of Maryland School of Medicine in Baltimore, working on molecular genetics of enteric bacteria. Her interests include clinical pharmacology and research on the pharmacology of antibiotics and natural products. She is studying antibiotic resistance and virulence characteristics of enteric organisms in Nigeria.

References

1. Kunin CM. Resistance to antimicrobial drugs—a worldwide calamity. Ann Intern Med 1993;118:557-61.
2. Murray BE, Alvarado T, Kim KH, Vorachit M, Jayanetra P, Levine MM, et al. Increasing resistance to trimethoprim-sulfamethoxazole among isolates of *Eschericha coli* in developing countries. J Infect Dis 1985;147:724-8.
3. Sack RB, Rahman M, Yunus M, Khan EH. Antimicrobial resistance in organisms causing diarrheal disease. Clin Infect Dis 1997;24 Suppl 1:S102-5.
4. Rahal K, Wang F, Schindler J, Rowe B, Cookson B, Huovinen P, et al. Reports on surveillance of antimicrobial resistance in individual countries. Clin Infect Dis 1997;24 Suppl 1:S169-75.
5. Hoge CW, Gambel JM, Srijan A, Pitarangsi C, Echeverria P. Trends in antibiotic resistance among diarrheal pathogens isolated in Thailand over 15 years. Clin Infect Dis 1998;26:341-5.

6. Bennish ML, Salam MA, Hossain MA, Myaux J, Khan EH, Chakraborty J, et al. Antimicrobial resistance of *Shigella* isolates in Bangladesh, 1983-1990: increasing frequency of strains multiply resistant to ampicillin, trimethoprim-sulfamethoxazole, and nalidixic acid. Clin Infect Dis 1992;14:1055-60.
7. Lima AA, Lima NL, Pinho MC, Barros Junior EA, Teixeira MJ, Martins MC, et al. High frequency of strains multiply resistant to ampicillin, trimethoprim-sulfamethoxazole, streptomycin, chloramphenicol, and tetracycline isolated from patients with shigellosis in northeastern Brazil during the period 1988 to 1993. Antimicrob Agents Chemother 1995;39:256-9.
8. Bogaerts J, Verhaegen J, Munyabikali JP, Mukantabana B, Lemmens P, Vandeven J, et al. Antimicrobial resistance and serotypes of *Shigella* isolates in Kigali, Rwanda (1983 to 1993): increasing frequency of multiple resistance. Diagn Microbiol Infect Dis 1997;28:165-71.
9. Dalsgaard A, Mortensen HF, Molbak K, Dias F, Serichantalergs O, Echeverria P. Molecular characterization of *Vibrio cholerae* O1 strains isolated during cholera outbreaks in Guinea-Bissau. J Clin Microbiol 1996;34:1189-92.
10. Mukhopadhyay AK, Garg S, Mitra R, Basu A, Rajendran K, Dutta D, et al. Temporal shifts in traits of *Vibrio cholerae* strains isolated from hospitalized patients in Calcutta: a 3-year (1993 to 1995) analysis. J Clin Microbiol 1996;34:2537-43.
11. Githui WA, Kwamanga D, Chakaya JM, Karimi FG, Waiyaki PG. Anti-tuberculous initial drug resistance of *Mycobacterium tuberculosis* in Kenya: a ten-year review. East Afr Med J 1993;70:609-12.
12. el Baghdadi J, Lazraq R, Ibrahimy S, Bouayad Z, Guinet R, Benslimane A. Survey of primary drug resistance of *Mycobacterium tuberculosis* in Casablanca, Morocco. International Journal of Tuberculosis and Lung Disease 1997;1:309-13.
13. Calva JJ, Sifuentes-Osornio J, Ceron C. Antimicrobial resistance in fecal flora: longitudinal community-based surveillance of children from urban Mexico. Antimicrob Agents Chemother 1996;40:1699-702.
14. Col NF, O'Connor RW. Estimating worldwide current antibiotic usage: report of Task Force 1. Rev Infect Dis 1987;9 (Suppl 3):S232-43.
15. Kunin CM, Johansen KS, Worning AM, Daschner FD. Report of a symposium on use and abuse of antibiotics worldwide. Reviews of Infectious Diseases 1990;12:12-9.
16. Guyon AB, Barman A, Ahmed JU, Ahmed AU, Alam MS. A baseline survey on use of drugs at the primary health care level in Bangladesh. Bull World Health Organ 1994;72:265-71.
17. Bojalil R and Calva JJ. Antibiotic misuse in diarrhea. A household survey in a Mexican community. J Clin Epidemiol 1994;47:147-56.
18. Nizami SQ, Khan IA, Bhutta ZA. Drug prescribing practices of general practitioners and paediatricians for childhood diarrhoea in Karachi, Pakistan. Soc Sci Med 1996;42:1133-9.
19. Paredes P, de la Pena M, Flores-Guerra E, Diaz J, Trostle J. Factors influencing physicians' prescribing behavior in the treatment of childhood diarrhoea: knowledge may not be the clue. Soc Sci Med 1996;42:1141-53.
20. Hui L, Li XS, Zeng XJ, Dai YH, Foy HM. Patterns and determinants of use of antibiotics for acute respiratory tract infection in children in China. Pediatr Infect Dis J 1997;16:560-4.
21. Reyes H, Guiscafre H, Munoz O, Perez-Cuevas R, Martinez H, Gutierrez G. Antibiotic noncompliance and waste in upper respiratory infections and acute diarrhea. J Clin Epidemiol 1997;50:1297-304.
22. Rodolfo J, Lozano J, Ruiz J, Londono D, Rodriguez M, Ruiz A. Drug prescription patterns of recently graduated physicians in Colombia [abstract]. J Clin Epidemiology 1997;50 Suppl 1:26S.
23. Muhuri PK, Anker M, Bryce J. Treatment patterns for childhood diarrhoea: evidence from demographic and health surveys. Bull World Health Organ 1996;74:135-46.
24. Cash R. Inappropriate treatment for dysentery. BMJ 1996;313:181-2.
25. Lee MG, Henry GL. Drug availability in Jamaica. West Indian Med J 1989;38:105-9.
26. Williams RJ, Heymann DL. Containment of antibiotic resistance. Science 1998;279:1153-4.
27. Turnridge J. Epidemiology of quinolone resistance. Eastern hemisphere. Drugs 1995;49:43-7.
28. World Health Organization. The use of essential drugs: model list of essential drugs: fifth report of the WHO Expert Committee, 1992. World Health Organ Tech Rep Ser 1992;825:1-75.
29. Mabadeje AF, Akintonwa AA, Ashorobi RB. The value and effects of implementing an essential drugs list in the Lagos University Teaching Hospital. Clin Pharmacol Ther 1991;50:121-4.
30. Munishi GK. The development of the Essential Drugs Program and implications for self-reliance in Tanzania. J Clin Epidemiol 1991;44 Suppl 2:7S-14S.
31. Hogerzeil HV, Bimo, Ross-Degnan D, Laing RO, Ofori-Adjei D, Santoso B, et al. Field tests for rational drug use in twelve developing countries. Lancet 1993;342:1408-10.
32. Salako LA. Drug supply in Nigeria. J Clin Epidemiol 1991;44 Suppl 2:15S-9S.
33. Gonzalez Ochoa E, Armas Perez L, Bravo Gonzalez JR, Cabrales Escobar J, Rosales Corrales R, Abreu Suarez G. Prescription of antibiotics for mild acute respiratory infections in children. Bull Pan Am Health Organ 1996;30:106-17.
34. Sturm AW, van der Pol R, Smits AJ, van Hellemondt FM, Mouton SW, Jamil B, et al. Over-the-counter availability of antimicrobial agents, self-medication and patterns of resistance in Karachi, Pakistan. J Antimicrob Chemother 1997;39:543-7.
35. Bexell A, Lwando E, von Hofsten B, Tembo S, Eriksson B, Diwan VK. Improving drug use through continuing education: a randomized controlled trial in Zambia. J Clin Epidemiol 1996;49:355-7.
36. Robles Y, Polack A. Continuing professional education in pharmacy in the Philippines 2. A current perspective. J Soc Admin Pharm 1997;14:24-132.
37. Ronsmans C, Islam T, Bennish ML. Medical practitioners' knowledge of dysentery treatment in Bangladesh. BMJ 1996;313:205-6.
38. Hartog R. Essential and non-essential drugs marketed by the 20 largest European pharmaceutical companies in developing countries. Soc Sci Med 1993;37:897-904.

39. Lee PR, Lurie P, Silverman MM, Lydecker M. Drug promotion and labeling in developing countries: an update. J Clin Epidemiol 1991;44 Suppl 2:49S-55S.
40. Pearson CA. The role of district hospitals and the action in international medicine network. Infect Dis Clin North Am 1995;9:391-405.
41. Thamlikitkul V. Antibiotic dispensing by drug store personnel in Bangkok, Thailand. J Antimicrob Chemother 1988;21:125-31.
42. Kigotho AW. Ugandan doctors request antibiotic moratorium. Lancet 1997;350:1014.
43. Dua V, Kunin CM, White LV. The use of antimicrobial drugs in Nagpur, India. A window on medical care in a developing country. Soc Sci Med 1994;38:717-24.
44. Singh J, Raje N. The rise of Western medicine in India. Lancet 1996;348:1598.
45. Haak H. Pharmaceuticals in two Brazilian villages: lay practices and perceptions. Soc Sci Med 1988;27:1415-27.
46. Kafle KK, Gartoulla RP, Pradhan YM, Shrestha AD, Karkee SB, Quick JD. Drug retailer training: experiences from Nepal. Soc Sci Med 1992;35:1015-25.
47. Rahman F, Andersson R, Svanstrom L. Medical help seeking behaviour of injury patients in a community in Bangladesh. Public Health 1998;112:31-5.
48. Fagbule D, Kalu A. Case management by community health workers of children with acute respiratory infections: implications for national ARI control programme. J Trop Med Hyg 1995;98:241-6.
49. Van der Geest S. Marketplace conversations in Cameroon: how and why popular medical knowledge comes into being. Cult Med Psychiatry 1991;15:69-90.
50. Wolff MJ. Use and misuse of antibiotics in Latin America. Clin Infect Dis 1993;17 Suppl 2:S346-S51.
51. Obaseiki-Ebor EE, Akerele JO, Ebea PO. A survey of antibiotic outpatient prescribing and antibiotic self-medication. J Antimicrob Chemother 1987;20:759-63.
52. Lansang MA, Lucas-Aquino R, Tupasi TE, Mina VS, Salazar LS, Joban N, et al. Purchase of antibiotics without prescription in Manila, the Philippines. Inappropriate choices and doses. J Clin Epidemiol 1990;43:61-7.
53. Okeke I, Lamikanra A. Quality and bioavailability of tetracycline capsules in a Nigerian semi-urban community. International Journal of Antimicrobial Agents 1995;5:245-50.
54. Hossain MM, Glass RI, Khan MR. Antibiotic use in a rural community in Bangladesh. Int J Epidemiol 1982;11:402-5.
55. Goel P, Ross-Degnan D, Berman P, Soumerai S. Retail pharmacies in developing countries: a behavior and intervention framework. Soc Sci Med 1996;42:1155-61.
56. Calva JJ, Ceron E, Bojalil R, Holbrook A. Antibiotic consumption in a community of Mexico City. II. Survey of purchases at pharmacies. Bol Med Hosp Infant Mex 1993;50:145-50.
57. Abosede OA. Self-medication: an important aspect of primary health care. Soc Sci Med 1984;19:699-703.
58. Shahid NS, Rahaman MM, Haider K, Banu H, Rahman N. Changing pattern of resistant Shiga bacillus (*Shigella dysenteriae* type 1) and *Shigella flexneri* in Bangladesh. J Infect Dis 1985;152:1114-9.
59. Yang YH, Fu SG, Peng H, Shen AD, Yue SJ, Go YF, et al. Abuse of antibiotics in China and its potential interference in determining the etiology of pediatric bacterial diseases. Pediatr Infect Dis J 1993;12:986-8.
60. Catalano M, Almiron MA, Romeo AM, Caruso E, Murtagh P, Harisiadi J. Comparison between parental report and results of microbiologic agar assay for presence of antibiotic in urine of Argentinian children with acute lower respiratory tract infection. Reviews of Infectious Diseases 1990;12 Suppl 8:S998-1000.
61. Kunin CM, Lipton HL, Tupasi T, et al. Social, behavioral, and practical factors affecting antibiotic use worldwide: report of Task Force 4. Reviews of Infectious Diseases 1987;9 Suppl 3:S270-S85.
62. Haak H, Hardon AP. Indigenised pharmaceuticals in developing countries: widely used, widely neglected. Lancet 1988;2:620-1.
63. Abellanosa I, Nichter M. Antibiotic prophylaxis among commercial sex workers in Cebu City, Philippines. Patterns of use and perceptions of efficacy. Sex Transm Dis 1996;23:407-12.
64. Strang JK. Tracing patients in rural Africa. Lancet 1996;348:1083-4.
65. Esezobo E, Offiong E. In vitro studies on some brands of oxytetracycline capsules available in Nigeria. Nigerian Journal of Pharmacology 1986;17:24-8.
66. Agom JK, Akanni AO, Dawodu TO. Quality of ampicillin/cloxacillin preparations on the Nigerian market. Nigerian Journal of Pharmacology 1990;21:36-8.
67. Taylor RB, Shakoor O, Behrens RH. Drug quality, a contributor to drug resistance? Lancet 1995;346:122.
68. Ballereau F, Prazuck T, Schrive I, Lafleuriel MT, Rozec D, Fisch A, et al. Stability of essential drugs in the field: results of a study conducted over a two-year period in Burkina Faso. Am J Trop Med Hyg 1997;57:31-6.
69. Hogerzeil HV, Battersby A, Srdanovic V, Stjernstrom NE. Stability of essential drugs during shipment to the tropics. BMJ 1992;304:210-2.
70. Shakoor O, Taylor RB, Behrens RH. Assessment of the incidence of substandard drugs in developing countries. Trop Med Int Health 1997;2:839-45.
71. Gustafsson LL, Wide K. Marketing of obsolete antibiotics in Central America. Lancet 1981;1:31-3.
72. Ali HM, Homeida MM, Abdeen MA. Drug dumping in donations to Sudan. Lancet 1988;333:538-9.
73. Berckmans P, Dawans V, Schmets G, Vandenbergh D, Autier P. Inappropriate drug-donation practices in Bosnia and Herzegovina, 1992 to 1996. N Engl J Med 1997;337:1842-5.
74. Guidelines for drug donations. Geneva: World Health Organization; 1996. Report No.: WHO/DAP/96.2.
75. Adjepon-Yamaoah K. Drugs for the tropics—their uses and abuses. Africa Health 1980;14-6.
76. Land T. Combating counterfeit drugs. Nature 1992;355:192.
77. McGregor A. Counterfeit drugs flood developing world. Lancet 1997;350:1690.
78. Alubo SO. Death for sale: a study of drug poisoning and deaths in Nigeria. Soc Sci Med 1994;38:97-103.
79. Couper MR. Strategies for the rational use of antimicrobials. Clin Infect Dis 1997;24 Suppl 1:S154-6.

80. Huang WF, Wen KC, Hsiao ML. Adulteration by synthetic therapeutic substances of traditional Chinese medicines in Taiwan. J Clin Pharmacol 1997;37:344-50.
81. Michel JM. Why do people like medicines? A perspective from Africa [letter]. Lancet 1985;1:210-1.
82. Ogungbamila FO, Ogundaini AO, editors. Traditional healing methods in the control and treatment of infectious diseases: report of a workshop on traditional healing methods in the control of infectious diseases. 1993 Jan 21-23; Obafemi Awolowo University, Ile-Ife, Nigeria.
83. Ogunbona FA, Akanni AO. Comparative bioavailability studies on some brands of ampicillin capsules. Pharmazie 1985;40:479.
84. Ali HM. Reduced ampicillin bioavailability following oral coadministration with chloroquine. J Antimicrob Chemother 1985;15:781-4.
85. Ogunbona FA, Oluwatudimu OO. Effect of a non-European (Nigerian) diet on the bioavailability of nitrofurantoin in man. Int J Pharmaecutics 1985;29:191-3.
86. Attef OA, Ali AA, Ali HM. Effect of Khat chewing on the bioavailability of ampicillin and amoxycillin. J Antimicrob Chemother 1997;39:523-5.
87. Johri RK, Zutshi U. An Ayurvedic formulation 'Trikatu' and its constituents. J Ethnopharmacol 1992;37:85-91.
88. Lamikanra A, Fayinka ST, Olusanya OO. Transfer of low level trimethoprim resistance in faecal isolates obtained from apparently healthy Nigerian students. FEMS Microbiol Lett 1989;50:275-8.
89. Murray BE, Mathewson JJ, DuPont HL, Ericsson CD, Reves RR. Emergence of resistant fecal *Escherichia coli* in travelers not taking prophylactic antimicrobial agents. Antimicrob Agents Chemother 1990;34:515-8.
90. Woolfson A, Huebner R, Wasas A, Chola S, Godfrey-Faussett P, Klugman K. Nasopharyngeal carriage of community-acquired, antibiotic-resistant *Streptococcus pneumoniae* in a Zambian paediatric population. Bull World Health Organ 1997;75:453-62.
91. Lamikanra A, Okeke IN. A study of the effect of the urban/rural divide on the incidence of antibiotic resistance in *E. coli*. Biomedical Letters 1997;55:91-7.
92. Implementation of the global strategy for health for all by the year 2000, second evaluation; and eighth report on the world health situation. Geneva: World Health Organization; 1992.
93. Korte R, Rehle T, Merkle A. Strategies to maintain health in the Third World. Trop Med Parasitol 1991;42:428-32.
94. Horton R. The infected metropolis. Lancet 1996;347:134-5.
95. Rosas I, Salinas E, Yela A, Calva E, Eslava C, Cravioto A. *Escherichia coli* in settled-dust and air samples collected in residential environments in Mexico City. Appl Environ Microbiol 1997;63:4093-5.
96. Meers PD. Infection control in developing countries. J Hosp Infect 1988;11 Suppl A:406-10.
97. Okello D, Konde-Lule J, Lubanga R, Arube-Wani J. Waste disposal in private medical clinics in Kampala, Uganda [abstract]. J Clin Epidemiol 1997;50 Suppl 1:45S.
98. ARI Program for the control of acute respiratory infections. Geneva: World Health Organization; 1994.
99. Shann F. The management of pneumonia in children in developing countries. Clin Infect Dis 1995;21 Suppl 3:S218-25.
100. Brown RC. Antibiotic sensitivity testing for infections in developing countries: lacking the basics [letter]. JAMA 1996;276:952-3.
101. Ringertz S, Muhe L, Krantz I, Hathaway A, Shamebo D, 0Freij L, et al. Prevalence of potential respiratory disease bacteria in children in Ethiopia. Antimicrobial susceptibility of the pathogens and use of antibiotics among the children. Acta Paediatr 1993;82:843-8.
102. Mastro TD, Ghafoor A, Nomani NK, Ishaq Z, Anwar F, Granoff DM, et al. Antimicrobial resistance of pneumococci in children with acute lower respiratory tract infection in Pakistan. Lancet 1991;337:156-9.
103. Andrews JM, Brown D, Wise R. A survey of antimicrobial susceptibility testing in the United Kingdom [letter]. J Antimicrob Chemother 1996;37:187-8.
104. Mutanda LN, Omari AM, Wamola IA. Adaptation of a method of measuring zone diameters of bacterial growth inhibition by antibiotics to suit developing countries. East Afr Med J 1989;66:441-7.
105. Shah VP. Trends in health, nutrition, and socio-economic status in Nigeria, India, and Brazil (1960-1990). J Trop Pediatr 1993;39:118-27.
106. Summerfield D. Health in the developing world. Health loses out to the arms trade. BMJ 1993;307:387.
107. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997;349:1436-42.
108. Dodge CP. Health implications of war in Uganda and Sudan. Soc Sci Med 1990;31:691-8.
109. Goma Epidemiology Group. Public health impact of Rwandan refugee crisis: what happened in Goma, Zaire, in July, 1994? Lancet 1995;345:339-44.
110. Marfin AA, Moore J, Collins C, Biellik R, Kattel U, Toole MJ, et al. Infectious disease surveillance during emergency relief to Bhutanese refugees in Nepal. JAMA 1994;272:377-81.
111. Cornwall J. Tuberculosis: a clinical problem of international importance. Lancet 1997;350:660-1.