Research

The antibacterial paradox: essential drugs, effectiveness, and cost

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The concept proposed by WHO of an essential drugs list that should comprise drugs corresponding to the health needs of the majority of the people has been embraced by countries, which have adapted it to their needs. In this study, the essential antibacterial drug lists of 16 countries chosen from the six WHO regions are reviewed. Most of these countries include 73% of WHO-recommended essential antibacterials on their lists. However, most are lacking reserve antibacterials, and even some main list antibacterials, which are essential when empirical therapy fails in cases of bacterial resistance. Many factors that may be responsible for the lack of selection of these drugs, not least cost considerations, are discussed.

Voir page 215 le résumé en français. En la página 215 figura un resumen en español.

Introduction

Infectious diseases, particularly sexually transmitted diseases (STDs), acute respiratory infections and diarrhoea, are the leading cause of mortality and morbidity in the developing world. In the past decade, human immunodeficiency virus (HIV) infections and acquired immunodeficiency syndrome (AIDS)-related complex may have led to a greater use of antibiotics, especially in children. Large amounts of money have been invested in research on anti-infective drugs, accounting for 16% of the total investment on drugs that reached the market place between 1972 and 1992, and placing this category of drugs in third place behind cardiovascular and nervous system drugs *(1)*. Antibiotics account for the highest proportion of the drug budget in many countries and constitute the largest group of drugs purchased in developing countries, where financial resources are scarce *(2)*. Slow economic growth and budgetary constraints in these countries have resulted in cuts in their health budgets.

The emergence of antibacterial-resistant strains of *Neisseria gonorrhoeae*, *Streptococcus pneumoniae*, *Shigella* spp., and *Salmonella* spp., caused by chromosomal mutations, plasmids, or transposons that can transfer resistance determinants in diverse bacteria species faster than new drugs can be developed to fight such resistance, may drive the cost of antibacterial therapy even higher. The traditional *N. gonorrhoeae* treatment with penicillins, which are safe and affordable, is fast becoming a thing of the past with the widespread appearance of penicillinase-producing *N. gonorrhoeae* (PPNG) strains. In Africa, 30–81% of patients with gonococcal infection carry PPNG strains *(3)*; and in South-east Asia, about 35% *(4)*. Strains have emerged that are highly resistant either singly or multiply to penicillins, tetracyclines, spectinomycin, erythromycin, and thiamphenicol *(5)*. Chromosomal resistance has rapidly made sulfonamides obsolete as antigonococcals, whereas plasmid resistance has compromised the antigonococcal value of penicillins and tetracyclines *(5)*. Thus, the emergence of *N. gonorrhoeae* resistance has narrowed down the choice of antibacterial treatment to ceftriaxone and the newer fluoroquinolones, which are expensive.

A total of 120 countries have adapted and implemented the list in their national drug policy *(6)*. This article reviews the antibacterial drugs in the essential drugs list of 16 countries chosen from the six WHO regions to assess their adequacy for coping with alternative therapy in the face of antibacterial resistance.

Methods

The current essential drugs lists of 16 countries in the six WHO regions, namely the African Region, the Region of the Americas, the Eastern Mediterranean Region, the European Region, the South-East Asian Region, and the Western Pacific Region, were reviewed. The lists were obtained from the WHO Action Programme on Essential Drugs. Individual countries included in this study are shown in Table 1. Most of the countries selected for this study, regardless of regional classification, include 165–

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592 (median, 249) drugs on their lists, which are meant for use at various levels of health care ranging from dispensaries to specialist hospitals (see Table 1) *(7–22)*.

The WHO essential drugs list is divided into two parts, main list drugs and complementary drugs. Main list and complementary drugs usually consist of therapeutic groups from which countries can select essential drugs. In the antibacterial category, there is a third group (reserve antibacterial agents); drugs in this group have no therapeutic alternatives, and their use is restricted to reducing the risk of developing resistance. The study did not differentiate between main list and complementary list drugs, since only two drugs (clindamycin and chloramphenicol oily suspension) are complementary. Substitutes were made for model list drugs in the same therapeutic categories; however, where there is more than one substitute, the substitutes are listed in the individual country lists only, and these lists were also reviewed.

Analysis of cost per course of treatment. The analysis of the cost per course of treatment was based on WHO treatment guidelines *(5, 23, 24)*, and did not include administrative costs or equipment and laboratory costs. Prices of antibacterial drugs, which did not include shipping and handling charges, were obtained from the *International drug price indicator guide — management science for health, 1996*, which provides an indication of the prices of generic drugs offered on the international market by nonprofit drug suppliers and procurement agencies. Prices of ceftriaxone and ciprofloxacin, which were not listed in the guide, were obtained from WHO.

Table 1: **Number of essential drugs, level of health care use, and coverage, per country**

Region/country (*ref.*)	No. of essential drugs	Level of health care use[a]
African		
Anglophone		
Botswana (*7*)	350	NA
Kenya (*8*)	195	RH, PH, DH, SDH, HC
Malawi (*9*)	242	HC, DH, C'H
Nigeria (*10*)	409	GH, PHI
Zimbabwe (*11*)	592	HC, DH, PH, SH
Francophone		
Benin (*12*)	187	HC, DH, PH, UH
Guinea (*13*)	165	U, RH, PH, HC
Mali (*14*)	198	NA
Americas		
Ecuador (*15*)	225	HC, DH, RH, SH
Honduras (*16*)	351	AH, R'H, NH, HC
Eastern Mediterranean		
Yemen (*17*)	256	4 levels[b]
European		
Estonia (*18*)	173	NA
South-East Asian		
Bhutan (*19*)	312	RH, DH, B, D
Sri Lanka (*20*)	220	HC, DH, PH, SH
Thailand (*21*)	366	NA
Western Pacific		
Philippines (*22*)	536	NA

[a] HC = health centre, D = dispensary, GH = government hospital, PHI = public health institute, RH = referral hospital, DH = district hospital, SDH = subdistrict hospital, PH = provincial hospital, UH or U = university hospital, SH = specialist hospital, AH = area hospital, CH = cantonal hospital, R'H = regional hospital, B = basic health units, C'H = central hospital, NA = not available.

[b] Not specified.

Results

Essential antibacterial drugs. On average, the countries chosen for the study selected 73% of the WHO main list and complementary antibacterial drugs.

Ampicillin, penicillinase-resistant cloxacillin, erythromycin, gentamicin, chloramphenicol, and sulfamethoxazole + trimethoprim appeared on all the lists (100% selection) of the 16 countries studied (see Table 2). In contrast to the WHO recommendation of using ampicillin injection only, different ampicillin formulations appeared on most of the lists. Ampicillin was mostly available as 250-mg capsules or tablets and as a 125-mg/ml suspension, as well as an injection formulation in some cases. However, amoxicillin capsules and tablets appeared on the lists of 75% of the countries studied.

Among the tetracyclines, the WHO model list includes only doxycycline. However, doxycycline or tetracycline appeared on most countries' lists, i.e. 75% (Table 2) and 68.8%, respectively. Both these tetracyclines were included on the lists of 31.2% of the countries studied, whereas the remaining 68.8% included either one or the other. Ecuador, Honduras, Mali, Nigeria, and Sri Lanka did not include doxycycline on their lists.

The quinolone, nalidixic acid, was selected by only 3 of 16 countries (18.8%) — Botswana, Philippines, and Yemen included it on their lists. The newer quinolone, ciprofloxacin, was listed by 62.5% of countries, but only Philippines and Yemen included both quinolones on their lists.

Trimethoprim was the least-selected antibacterial drug. The combination drug sulfamethoxazole + trimethoprim was preferred to the single drug trimethoprim, since only 2 of the 16 countries — Botswana and Zimbabwe — included it on their lists. These countries listed both trimethoprim alone and in combination with sulfamethoxazole, whereas the other countries listed the combination.

Sulfadimidine appeared in 31.3% (5 out of 16) of the lists, and metronidazole in 81.3%. Although erythromycin was included in every list, clindamycin appeared in 43.8% of the lists. Spectinomycin was listed by 37.5% of the countries (see Table 2). Only 43.6% of the countries studied listed the reserve antibacterial third-generation cefalosporins, ceftriaxone, or ceftazidime (Table 2). Although first- and

second-generation cefalosporins do not appear on the WHO list, Benin, Bhutan, Botswana, Malawi, and Thailand listed them, whereas Mali, Sri Lanka, and Yemen did not. The most commonly listed first- and second-generation cefalosporins were cefalexin (31.3%) and cefoxitin (25%).

Vancomycin, another reserve antibacterial, was only included in the essential drugs lists of Botswana and Honduras. The frequency of selection was 12.5% (see Table 2). The data showed that 38–88% of the countries studied listed neither vancomycin, ceftriaxone, spectinomycin, nor quinolones.

Other antibacterials included on the countries' lists, but which differed from those mentioned above, were piperacillin (31.3%), aminoglycoside alternatives to gentamicin — neomycin, amikacin, and kanamycin (each on 25% of lists) — and ampicillin combinations (18.8%).

Costs per course of treatment of empirical therapy and in cases of bacterial resistance. Table 3 shows costs per course of treatment for STDs; highlighted are increases in treatment costs resulting from bacterial resistance. For cases of nonresistant *N. gonorrhoeae* ano-genital infections that respond to penicillin, tetracyclines, or sulfonamides, the cost per course of treatment is less than US$ 1, whereas in resistant cases treated with ceftriaxone, ciprofloxacin, or spectinomycin, the cost is over US$ 2 and may be as high as US$ 7 depending on the drug.

Cost comparisons of drugs used to combat drug-resistant strains, shown in Table 4, indicate that, on the one hand, the most expensive of these drugs, spectinomycin, is 15 times more costly than doxycycline and at least 10 times more so than procaine benzylpenicillin. On the other hand, ciprofloxacin, the least expensive of the drugs, is 4–6 times more expensive than procaine benzylpenicillin, amoxicillin, or doxycycline.

Syphilis, an STD with no known resistant strains, still responds well to penicillin treatment. It costs less to cure than antibacterial-resistant gonorrhoea. Treatment of syphilis costs under US$ 0.50 with benzathine benzylpenicillin (Table 3), whereas with procaine benzylpenicillin the cost is a little over US$ 1.

Similarly, empirical treatment of nonresistant cases of pneumonia with sulfamethoxazole + trimethoprim, procaine benzylpenicillin, amoxicillin, and ampicillin costs US$ 0.08, 0.21, 0.26, and 0.66, respectively, whereas a day's treatment of methicillin-resistant *S. pneumoniae* with vancomycin costs US$ 7.32, 11–90 times more than nonresistant cases.

For cases of adult shigellosis that are resistant to ampicillin, chloramphenicol, sulfamethoxazole + trimethoprim, tetracycline, and nalidixic acid, the cost of a 5-day course of treatment with ciprofloxacin is US$ 26.70. This is 86 times more expensive than treatment with sulfamethoxazole + trimethoprim (US$ 0.31) and 10–11 times more so than treatment with ampicillin (US$ 2.61) or nalidixic acid (US$ 2.36).

Table 2: **Frequency of selection of WHO model list antibacterials by 16 countries selected from all six WHO regions**

Antibacterial	Frequency of selection (%)
Penicillins	
Ampicillin[a]	100
Cloxacillin	100
Benzathine benzylpenicillin	93.8
Benzylpenicillin	87.5
Phenylmethoxypenicillin	87.5
Procaine benzylpenicillin	81.3
Amoxicillin	75
Chloramphenicols	
Chloramphenicol	100
Aminoglycosides	
Gentamicin	100
Tetracyclines	
Doxycycline	75
Macrolides	
Erythromycin	100
Lincosamides	
Clindamycin	43.8
Sulfonamides	
Sulfamethoxazole + trimethoprim	100
Sulfadimidine	31.3
Trimethoprim	12.5
Furans	
Nitrofurantoin	75
Quinolones	
Ciprofloxacin	62.5
Nalidixic acid	18.8
Others	
Spectinomycin	37.5
Metronidazole	81.3
Restricted antibacterials	
Third-generation cefalosporins	
Ceftriaxone	37.3
Ceftazidime	6.3
Others	
Vancomycin	12.5

[a] Available mainly as capsules and tablets.

Discussion

The review of the essential drugs lists of 16 countries in the WHO African Region, the Region of the Americas, South-East Asia Region, Western Pacific Region, Eastern Mediterranean Region, and European Region showed that these countries have adopted over 70% of the WHO model list antibacterials. Essential drugs lists are intended to aid decision-making on drug procurement and supply to serve the health care needs of the majority of the population. In addition, essential drugs lists reduce duplication, help to make health care budgeting and spending more efficient, and promote rational prescribing.

However, the review showed that 33–88% of the countries do not include cefalosporins, fluoroquinolones, vancomycin, spectinomycin, trimetho-

Table 3: **Cost per treatment course of nonresistant and resistant *N. gonorrhoeae* infections and syphilis**

STD	Treatment	Cost per treatment course (US$)
Gonorrhoea	Ceftriaxone (250-mg IM single dose)	4.98
Ano-genital	OR spectinomycin (2 g single dose)	6.87
infection	OR ciprofloxacin (500 mg orally single dose)	2.67
Not penicillin-,	Amoxicillin (3 g orally) plus	0.57
tetracycline-,	probenecid 1 g	
or sulfonamide-	OR procaine benzylpenicillin	0.68
resistant	(4.8 mIU, IM) plus probenecid	
	OR doxycycline (100 mg orally twice daily)	0.45
	OR tetracycline (500 mg orally thrice daily x 7 days)	0.58
	OR sulfamethoxazole (400 mg) + trimethoprim (80 mg) (10 tablets twice daily x 3 days)	0.47
Syphilis	Benzathine benzylpenicillin (2.4 mIU	0.36
Early syphilis	single dose)	
	OR procaine benzylpenicillin (1.2 mIU four times daily x 7 days)	1.27

Table 4: **Cost ratio of drugs used to combat *N. gonorrhoeae*-resistant cases to those used in nonresistant cases**

Drug	Ceftriaxone	Spectinomycin	Ciprofloxacin
Doxycycline	11.1	15.3	5.9
Procaine benzylpenicillin	7.3	10.1	3.9
Tetracycline	8.6	11.8	4.6
Amoxicillin	8.7	12.1	4.7
Sulfamethoxazole + trimethoprim	10.6	14.6	5.7

prim, nalidixic acid, or piperacillin on their lists. Of particular concern is the absence of cefalosporins, fluoroquinolones, and spectinomycin, which are useful in the treatment of resistant cases of meningitis, gonorrhoea, *Salmonella* infection, and shigellosis, all of which are of epidemiological importance. Cefalosporins, especially third generation, are useful for treating penicillin- or chloramphenicol-resistant *Haemophilus influenzae* type b meningitis, penicillin- or spectinomycin-resistant gonorrhoea, or tetracycline- or sulfamethoxazole + trimethoprim-resistant *H. ducreyi* chancroid. Fluoroquinolones are indicated in shigellosis and *Salmonella*-resistant cases when initial empirical therapy fails *(6)*. They are also alternatives to cefalosporins in cases of gonorrhoea and chancroid when oral therapy is necessary, or in hospital-acquired infections caused by Gram-negative bacilli such as *Escherichia coli*, *Klebsiella* spp., and *Pseudomonas aeruginosa*, or to vancomycin in cases of meticillin-resistant *Staphylococcus aureus (6)*.

What factors might contribute to the failure of countries to select the above-mentioned drugs? First, cost considerations may be an important factor. For infectious diseases caused by bacterial strains resistant to initial empirical therapy, newer antibacterial treatments are needed, but they come at a price. Expensive antibacterial drugs may not be affordable to all in developing countries, for example in sub-Saharan Africa, where out-of-pocket expenses make up 40% of the health care costs *(25)*. Patients have been known to drop out of treatment because of its cost *(26, 27)*. The paradox is that people who can least afford treatment are those most vulnerable to infections.

Other factors that might play a role in not selecting reserve antibacterials for resistant cases are the absence of laboratory facilities to test for bacterial susceptibility; lack of prescriber education on antimicrobial treatment and resistance; promotional activities by pharmaceutical companies; and the failure of countries to review their essential drugs list to reflect the results of current antibacterial susceptibility testing.

More important, the failure to properly select reserve antibacterial agents has health care implications. An increase in bacterial resistance would entail increases in direct and indirect health care costs that most developing countries can ill afford, for example increased morbidity and mortality, particularly in immunocompromised patients, and decreased productivity due to absence from work.

Preventive measures to control the spread of resistant strains would in the long term be the most cost-effective way to reduce the burden of bacterial resistance on the health care system. The emergence of resistance to antimicrobial agents may be delayed by reducing use of such drugs. Education of all parties involved is necessary. In this regard, educating prescribers, patients, and pharmacists — especially community pharmacists, from whom most over-the-counter antibiotics are purchased — is essential. Other preventive measures include arresting the dissemination of resistant strains through good hygienic practices and avoiding agents that select for resistance genes *(28)*. Such measures would delay emergence of bacterial resistance and reduce reliance on newer and expensive antimicrobial agents.

Computerized surveillance networks such as the WHONET provide data on regional antibacterial susceptibility patterns, which if regularly disseminated to prescribers would improve the empirical selection of antimicrobial agents, help to develop treatment guidelines on antimicrobial agents useful for national programmes, and provide prompt treatment with newer agents to combat bacterial resistance *(29)*.

In conclusion, the fight against antimicrobial resistance can be likened to a revolving door, in which the optimal treatment for the patient with a resistant strain has the effect of increasing use of reserve drugs, and thereby speeding up selection in the population of strains resistant to these drugs as well,

compromising them for future patients. Strains of *S. aureus* resistant to vancomycin are already appearing *(30),* as well as strains resistant to fluoroquinolones, whose introduction 10 years ago for wide-spectrum activity led to their extensive use and misuse. ■

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Résumé

Le paradoxe antibactérien : médicaments essentiels, efficacité et coût

L'article passe en revue les listes d'antibactériens essentiels établies par 16 pays choisis dans les six Régions de l'OMS. Parmi les antibactériens essentiels retenus par la plupart des pays, figurent les pénicillines, les tétracyclines, les aminoglycosides, les sulfamides et les macrolides. Ces produits sont adaptés au traitement des affections respiratoires aiguës, des maladies diarrhéiques et des MST pour lesquelles il n'existe pas de pharmacorésistance multiple. Ce sont ces maladies qui sont responsables de l'augmentation de la morbidité et de la mortalité dans les pays en développement. Pour inverser cette tendance, on fait un usage croissant des antibactériens. Ces produits représentent les deux tiers des médicaments utilisés dans les pays en développement.

Cependant, la résistance croissante opposée par les bactéries aux antibiotiques limite l'utilité de certains de ceux qui figurent sur les listes établies par ces pays. Une liste de médicaments essentiels où ne figurent ni les céphalosporines de troisième génération, ni les fluoroquinolones, ni la spectinomycine, ni la vancomycine peut-elle encore servir à quelque chose en cas de polypharmacorésistance ?

On a pu montrer que l'augmentation du coût de certains traitements consécutive à ce problème de pharmacorésistance conduit à une moins bonne observance. On a procédé à une analyse du coût par cure pour déterminer l'effet de la pharmacorésistance sur le prix de revient du traitement. Les résultats obtenus montrent que le recours à des produits nouveaux comme les fluoroquinolones ou les céphalosporines par suite de l'échec des pénicillines, des sulfamides ou des tétracyclines a eu pour effet d'augmenter le coût d'une cure dans des proportions astronomiques. Cet état de choses vient encore accroître la charge que les soins de santé représentent pour les pays en développement, charge que certains d'entre eux ne sont guère en mesure de supporter. L'auteur discute les implications sanitaires de la pharmacorésistance des bactéries et les mesures à prendre pour ralentir la propagation des souches résistantes.

Resumen

La paradoja de los antibacterianos: medicamentos esenciales, eficacia y costo

Se procedió a revisar las listas de medicamentos antibacterianos esenciales de 16 países seleccionados entre las seis regiones de la OMS. Entre los antibacterianos esenciales de la mayoría de esos países figuran las penicilinas, las tetraciclinas, los aminoglucócidos, las sulfamidas y los macrólidos. En ausencia de polifarmacorresistencia esos antibióticos son adecuados para tratar las infecciones respiratorias agudas, las enfermedades diarreicas y las ETS. Estas enfermedades son las que más contribuyen a la mayor morbilidad y mortalidad observada en los países en desarrollo. A fin de invertir esa tendencia, se recurre cada vez más a medicamentos antibacterianos, los cuales representan las dos terceras partes de los fármacos empleados en esos países.

No obstante, el aumento de la resistencia bacteriana limita la utilidad de algunos de los antibacterianos que figuran en las listas de esos países. En caso de polifarmacorresistencia, ¿hasta qué punto puede ser útil una lista de medicamentos esenciales que omita las cefalosporinas de tercera generación, las fluoroquinolonas, la espectinomicina o la vancomicina?

Hay pruebas de que el aumento del costo de algunos tratamientos que ocasiona la resistencia bacteriana puede traducirse en una mala observancia del régimen prescrito. Se llevó a cabo un análisis del costo por tratamiento para determinar el efecto de la farmacorresistencia en los costos terapéuticos. Los resultados mostraron que la administración de productos más recientes, como fluoroquinolonas o cefalosporinas, tras el fracaso de un tratamiento previo con penicilinas, sulfonamidas o tetraciclinas aumentaba el costo del tratamiento de manera astronómica. Ello grava aún más la asistencia sanitaria en la mayoría de los países en desarrollo, cosa que mal pueden permitirse. Se analizan las repercusiones sanitarias de la resistencia bacteriana y las medidas que permiten reducir la propagación de las cepas resistentes.

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