Antibiotic Resistance in Africa –

Discerning the enemy and plotting a defense

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At the turn of the century, the World Health Organization estimated that infections

accounted for 45% of deaths in Africa and South-East Asia and that these diseases were

responsible for 48% of premature deaths worldwide. Bacteria cause a significant

proportion of infections in Africa. Unfortunately, in a remarkably short time, resistance to

antibiotics has undermined the idealistic hope that bacterial infection would cease to be an

important cause of death and disease. Indeed, antibiotic resistance increasingly

compromises the outcome of many infections that were, until recently, treatable and

remain the most common diseases in Africa. For example, as shown in Table 1, resistant

tuberculosis (TB) infections are highly prevalent in some African countries [1]. High

resistance rates can often be correlated to the absence of properly implemented control

programs such as directly observed treatment, short-course (DOTS) schemes [3]. In a

survey conducted in an area of Cameroon that lacks a fully functional TB control program,

multi-drug resistance TB was observed in 27.6% of the patients with a previous history of

treatment [4].

TB is a pertinent case in point because it is highly prevalent in many African and other

developing countries [5] but many other bacterial infections are severely compromised by

resistance. These include diseases caused by to Gram-negative enteric rods, respiratory

infections, bacterial meningitis, sexually transmitted diseases as well as hospital acquired

infections. Due to the widespread distribution of penicillinase-producing *Neisseria*

gonorrhea, penicillin or ampicillin can no longer be employed in the empiric management

of gonorrhea [6, 7]. The prevalence of gonococcal resistance to affordable alternatives -

such as tetracyclines, thiamphenicol and spectinomycin - continues to rise and resistance to

fluoroquinolones has emerged [6]. The picture is similar with other organisms. Reports from different parts of Nigeria have observed temporal trends in the prevalence of resistance among enteric organisms, such as *Escherichia coli* and *Shigella* (Figure 1). In multiple studies, resistance to commonly used antimicrobials, including trimethoprim-sulphamethoxazole (TMP-SMX, also known as cotrimoxazole), ampicillin, tetracycline and chloramphenicol has shown increasing prevalence in the last 15 years [8, 9]. These studies have consistently found low prevalence of resistance to nalidixic acid and the fluoroquinolones, however, an upward trend has recently been observed with these agents. Studies in other parts of the world, where fluoroquinolones are more commonly employed, have revealed that routine use of these drugs is often associated with a rapid increase in the proportion of resistant strains [10]. The antibiotic paradox is also repeated in many other pathogen-human interactions, including antimalarial resistance in *Plasmodium* spp. and HIV antiretroviral resistance, as well as insecticide resistance in insect vectors. Lessons that can be learned from antibiotic resistance can be applied to these paradigms as well.

Historically, resistance to antimicrobials has been seen for all agents, soon after their discovery (Figure 2). Not long after he discovered penicillin, Nobel laureate Alexander Flemming identified Staphylococci that were resistant to the first 'wonder drug'. He correctly predicted that imprudent use of antibiotics could lead to clinical failures with these drugs in the future. Until this time, all Staphylococci were considered sensitive to penicillin and many Gram-negative organisms known to be were intrinsically resistant. Intrinsic resistance poses few problems for clinicians. It is the traditionally unexpected acquired resistance - resistance in a species originally considered sensitive - that can result

in dreaded chemotherapeutic failure. Since Fleming's report, the valuable life span of

virtually every antibiotic has been diminished by the acquisition of resistance in bacteria

(Figure 2).

Bacterial strains that are resistant to an antibiotic can produce enzymes that inactivate the

drug, are impermeable to it, actively export it from the cell or by-pass the cellular target the

agent interferes with. Bacteria acquire the ability to do this by altering their own genes

(through mutation) or, more commonly, by horizontally acquiring 'ready made' resistance

genes from other organisms. Horizontally acquired resistance genes are often carried on

transmissible plasmids, small rings of DNA that are efficiently transferred from one cell to

another by mating or conjugation. Some antibiotic resistance genes are held within mobile

elements called transposons or integrons. These elements not only capture and organize

the expression of resistance genes; they are also capable of moving from plasmids to the

chromosome, a feature that stabilizes their inheritance.

In general, the acquisition of foreign DNA or mutations provides little advantage for a

bacterial cell unless there is express need for the phenotype encoded by the new genes.

Therefore, bacteria harboring resistance genes are given selective advantage over those that

do not only in the presence of the antibiotic in question. If a population of bacteria

comprised predominantly of susceptible strains, with a few resistant ones is exposed to an

antibiotic, the sensitive strains are killed off. The resistant ones are left to flourish,

replacing the old population. This simple fact has been responsible for the success of

resistant bacteria in a world where antibiotics are used for a broad range of purposes. One

example of unnecessary use is the application of antibiotics as growth promoters (sometimes known as digestive enhancers) in animal husbandry. This exposes many more bacteria to selective pressure than human use with little rationale.

The use of antibiotics at recommended dosage levels to treat confirmed bacterial infections is a type of exposure for which the benefit far outweighs the risk of selecting resistant strains. This type of acceptable selection pressure is high in many African countries where there is a heavy burden of community-acquired infectious diseases, which dictates a heavy requirement for curative therapy for bacterial infections. Unfortunately, much of the antibiotic therapy is not laboratory-individualized or even by laboratory-extrapolated. This, coupled with the high proportion of life-threatening infections that require immediate treatment, means that antibiotic prescription is largely empirical and that resistance will often only be detected by therapeutic failure. The treatment of infected people in many parts of Africa is further challenged by the fact that the prohibitive cost of newer antimicrobials, when available, places them out of the reach of majority of patients. In many health centers in sub-Saharan Africa, the repertoire of first-line drugs is limited to ampicillin, chloramphenicol, erythromycin, gentamicin, penicillin, tetracycline and trimethoprim-sulphathoxazole. The available second line antibiotics vary with locality but will often include amikacin, amoxicillin-clavulanic acid, cefuroxime, ciprofloxacin and nalidixic acid [12, 13]. It is particularly disconcerting to note that a number of countries do not have a broad enough selection of second-line drugs and so would have difficulty managing resistant infections [12]. Even when not available for individualized patient care, surveillance susceptibility testing is a valuable tool for cost-effective customization of

empiric antibiotic therapy. For example, many prescribers use antibiotics that are no longer effective due to increased prevalence of resistance, eventually requiring multiple chemotherapeutic courses to effect a cure. Conversely, expensive agents that are employed in life-threatening situations may be substituted for cheaper agents, if local susceptibilities are known [14, 15]. The cost of resistance is difficult to compute and generally underestimated. The estimated monetary cost of antimicrobials required to treat a resistant *N. gonorrheae* infection is 2-7 times greater than a non-resistant infection. This multiple is 10-11 times for Shigellosis in adults and as much as 11-90 times for resistant *Streptococcus pnemoniae*. Further, hidden, costs accrue from longer hospital admission time, increased opportunity for pathogen transmission and reduced productivity due to prolonged illness. More serious and more difficult to quantify are the costs arising from mortality. These devastating consequences of resistance are seen increasingly more frequently during outbreaks of life-threatening diseases such as cholera and dysentery. The outbreaks listed in Table 2 featured case-fatality rates in the range of 10%, due in a large part to antibiotic resistance.

The AIDS epidemic has created an even greater need for both preventive and curative antibiotic therapy as well as a sub-population highly susceptible to infection, which supplies hosts for multiply-resistant strains of problematic organisms such as *Mycobacterium tuberculosis*. UNAIDS/WHO estimates suggest that over 20 million Africans are infected with HIV. Although the prevalence of resistance among TB isolates in Africa is high, but not greater than in other parts of the world [3], the highest rates of HIV-TB infection are also seen in Africa with over 30% of TB cases being HIV-positive

[22]. It is essential that preventive measures are put in place to prevent the escalation of resistance rates to a level seen in countries like Russia, since most African countries cannot afford the prohibitive monetary costs of treating these infections or the high mortality rates they cause[3].

Other unresolved chemotherapeutic dilemmas have arisen as a result of the AIDS epidemic. For example, there is inconclusive evidence to support or refute the use of TMP-SMX for the prevention of opportunistic infections in AIDS patients [23]. Although this drug combination is one that would be affordable to many patients, it is a valuable first-line treatment of a wide range of bacterial infections. Therefore use, and consequently selection pressure, is already excessive for TMP-SMX. Resistance to this combination is becoming increasingly prevalent and it is thought that additional pressure from prophylactic use could abrogate the useful lifespan of the drug. The effects could be broader than consequences for antibacterial therapy, since there is evidence to suggest that this drug could contribute to selective pressure for the pyrimethamine-sulfadoxine combination, the drug of choice for malaria in many areas [24]. There are also conflicting data with regard to the reduction of mortality in AIDS patients. Clearly, more studies in this area are required before these important policy decisions can be made.

When antibacterial drugs are used imprudently, such as to treat infections caused by parasites (for example, malaria) or viruses (such as the common cold), they provide no benefit to the patient and provide selective pressure with possible needless adverse consequences for the community. Prescribers should resist the pressure from patients to

proffer antibiotics unless they can make a diagnosis of bacterial infection. Studies from around the world have shown that between 40 and over 90% of antibiotic prescriptions are unnecessary. In many parts of Africa, where antibiotics are commonly available from unsanctioned providers, it will be worth educating the general populace about the consequences of irrational antibiotic resistance. Unsanctioned providers often reach out to people with limited access to orthodox health care, and are commonly not trained to diagnose infections or correctly prescribe appropriate doses. They however serve as an unofficial outlet for many antibiotics, often capsules and tablets of cheaper antimicrobials, but are not limited to these. For example, Becker et al [25] recently described the inappropriate distribution of injectable antibiotics, including second- and third-line drugs such as oxacillin and third-generation cephalosporins, medicines that should be conserved for managing resistant infections.

The use of sub-therapeutic doses creates a situation where highly resistant strains can be selected sequentially and this is a condition that prevails in many cases when antibiotics are used without proper prescription or in patient non-compliance. Poor quality drugs can provide sub-inhibitory selective pressure, of which neither the patient nor the prescriber are aware. Reports of sub-standard antibiotics have come from many countries and a significant proportion of these are in Africa. These reports describe preparations containing anything between 0-80% of stated label claim. Some of them contain such low concentrations that they can only be considered counterfeit, i.e. deliberately manufactured with low or no active drug content. Others may have complied with pharmacopoeia standards at some time but have, in the course of distribution and display, been degraded

by heat and humidity. Where possible, patients must be advised of the wisdom of obtaining medicines at reputable outlets, where they have been properly stored and where expiration and lot information is available.

In addition to providing selection pressure, humans have encouraged resistance among bacteria by creating conditions suitable for bacterial multiplication and the exchange of genetic material. Warm, moist and unclean environments are conducive for the spread of pathogens, but they also encourage the spread of resistant organisms that may not be pathogenic. These organisms often carry resistance genes that can be spread to pathogens and therefore constitute a hidden reservoir of antibiotic resistance. Surveys of healthy people have shown that they often carry large proportions of resistant *Escherichia coli* in their gastro-intestinal tracts, for example [8, 9]. The rising prevalence of resistance in these organisms over time has been correlated to resistance in clinical *Salmonella* or *Shigella* enteritis in the same environment. Furthermore, hygiene, sanitation and infection control programs help to prevent the spread of resistant agents, reducing the need for antibiotics in the first place.

In hospitals, the antibiotic pressure is necessarily high and the close proximity of ill people, being cared for collectively provides an environment where resistant strains can be selected and rapidly spread to susceptible patients. The WHO records that the United States of America spends about US$10 billion a year dealing with this problem. Particularly problematic organisms are methicillin resistant staphylocci, and multiply resistant gram-negative rods. As many of the species that cause outbreaks of hospital-

acquired infection are part of the normal flora of healthy carriers, it is feasible that an

upsurge of resistance among community isolates will be associated with an increasing

frequency of hospital outbreaks. Overcrowding and lack of resources for effective

infection control, common in many hospitals, are fuel for hospital epidemics of these

organisms. In an outbreak of resistant *Acinetobacter* in a South African hospital, mortality

was over 50% [26] and outbreaks of life threatening diarrheal disease have occurred in

hospitals, associated with similar rates of mortality [27]. Recent reports have indicated

that vancomycin-resistant (or in some cases, -intermediate) Staphylococci are being

recovered from multiple sites worldwide. One of these sites is Johannesburg, South

Africa, where alarmingly, intermediately vancomycin resistant *S. aureus* was recently

isolated from two patients [28]. While it is hoped that these organisms are not widespread

on the continent, it is possible that the lack of reports from elsewhere on the continent is

due to inadequate surveillance, rather than complete absence.

Several new strategies have been proposed to halt the alarming trend of resistance and to

deal with the ever-increasing number of infections caused by multiply resistant organisms.

Although many earlier antibiotic discovery programs were abandoned when it was thought

that bacterial infections would decline in importance, investigators have now been spurred

to resume this line of research. Efforts are now underway to develop antimicrobials with

novel mechanisms of action. These efforts will be greatly aided by the rapidly

accumulating bank of microbial genome sequences and will permit the use of

bioinformatics and genomic techniques to identify and study new targets. Other

investigators are looking to develop alternatives to antibiotics such as bacteriophage-

derived therapy or chemical agents that can block or reverse resistance pathways. It is also possible that new agents will be found in natural products, an age-old source of antimicrobials. Alternatives to antimicrobials for the prevention and treatment of bacterial infection are also development priorities. Current research is focusing reducing the need for antibiotics by developing vaccines and probiotics [29] and implementing public health strategies. Most of these initiatives are recent and their development will be a long-term process, during which microbes continue to acquire new strategies for resistance. Clearly, prudent use of antibiotics and infection control, sanitation and hygiene practices are steps that must be taken now to stem the trend of rising resistance. These are all focus areas of the WHO global strategy for containment of antimicrobial resistance [30][‡], which was released in 2001. In particular, adopting prudent practices will conserve the efficacy of the drugs of the future. Responsibility for instituting and maintaining programs that will optimize antimicrobial therapy lies with health workers who are in a better position to understand the devastating consequences of acting otherwise. In countries all over the world, many are organizing chapters of the Alliance for Prudent Use of Antibiotics[§] to identify and address the priority areas in their own countries and to map out locally relevant strategies for combating the problem. No time must be lost. Resistant bacteria began the war almost a century ago and clearly have acquired an edge. If they are to be overcome, they must be resisted now.

[‡] The executive summary, complete WHO global strategy for containment of antimicrobial resistance and background documents are available from the World Health Organization's website at http://www.who.int/emc/amr.html

[§] For more information about an APUA chapter near you, visit the APUA website www.apua.org or e-mail Anibal Sosa at: anibal.sosa@tufts.edu

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Table 1: Drug-resistant tuberculosis in Africa

Adapted from Mwinga (2002) [2]

	Percentage of strains resistant to			
Country	1 drug	2 drugs	3 drugs	4 drugs
CAR	12.1	6.1	5.2	3.0
Guinea	9.4	12.5	15.6	12.5
Kenya	30.4	6.5	0	0
Lesotho	20.8	5.7	5.7	1.9
Mozambique	22.1	21.3	0.8	0.8
Uganda	28.9	20.0	2.2	0
Zimbabwe	5.6	5.6	2.8	0

Table 2: A selection of African epidemics of acute bacteria infections that have been worsened by antibiotic resistance.

Country	Year	Disease (causative organism)	Antibiotic resistance pattern	References
Somalia	1985-86	Cholera (*Vibrio cholerae*)	ampicillin, kanamycin, streptomycin, sulfonamide, and tetracycline	[16]
Rwanda	1994	Cholera and bacillary dysentery (*V. cholerae and S. dysenteriae*)	ampicillin, chloramphenicol, sulfonamides, tetracycline and trimethoprim	[17]
South Africa	1995	Bacillary dysentery	ampicillin, chloramphenicol, sulfonamides, tetracycline and trimethoprim	[18]
Nigeria	1995	Cholera	chloramphenicol, spectinomycin, sulfonamides, trimethoprim	[19]
Guinea Bissau	1996-97	Cholera	ampicillin, aminoglycosides, erythromycin, nalidixic acid, sulfamethoxazole, tetracycline and trimethoprim	[20]
Madagascar	1997	Plague (*Yersinia pestis*)	ampicillin, chloramphenicol, kanamycin, streptomycin, spectinomycin, sulfonamide, and tetracycline	[21]

Figure 1: Percentage of *E. coli* isolates from healthy adults resistant to commonly-used antibiotics (1986-1998).
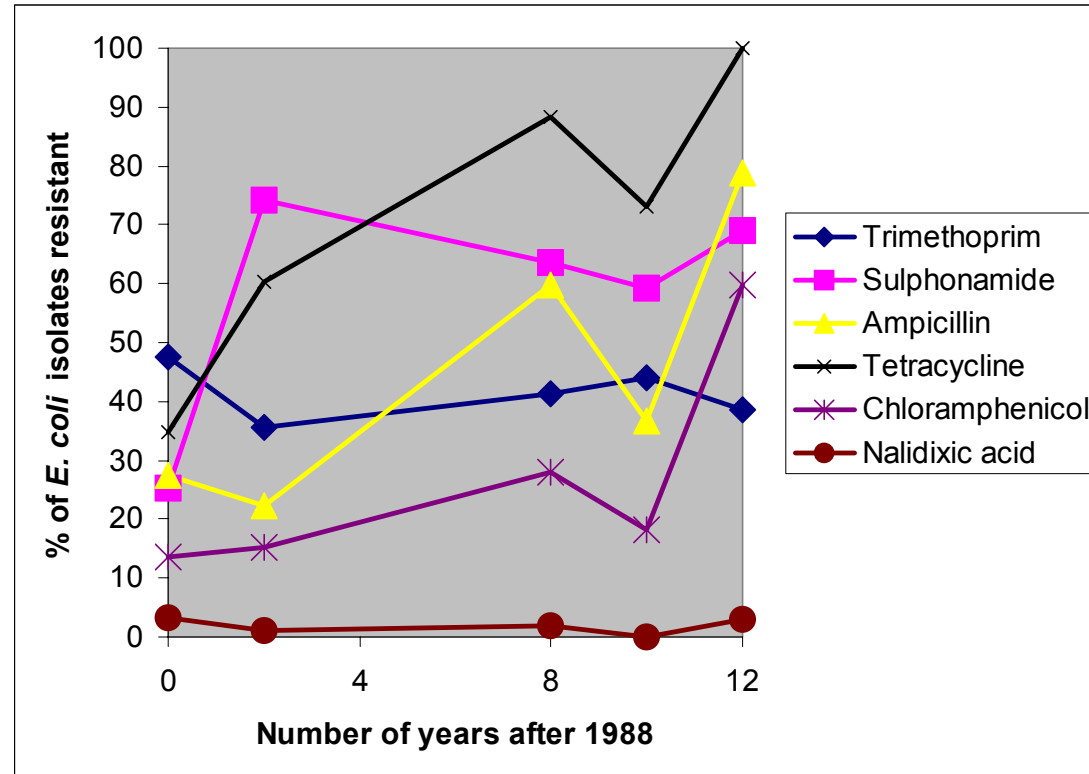
Adapted from [8]

Figure 2: The intervals between antibiotic discovery and the development of resistance (adapted from [11])