Chapter 32

Antimicrobial Resistance and its Containment in Developing Countries

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1. INTRODUCTION

Antimicrobial resistance (AR) is a complex problem and a big challenge to public and animal health globally. In the last several years, the frequency and spectrum of antimicrobial-resistant infections have increased in both animals and man in developed nations and the developing countries (DCs) (Andrade *et al*., 2003; Ashkenazi *et al*., 1995; Bennish *et al*., 1992; Bogaerts *et al*., 1997; Daniels *et al*., 1999; Filius and Gyssens, 2002; Flournoy *et al*., 2000; Gupta *et al*., 2001; Russo and Johnson, 2003). This increasing frequency is attributed to a combination of microbial characteristics, selective pressures of antimicrobial use, and societal and technologic changes that enhance the development and transmission of drug-resistant organisms (Aarestrup *et al*., 2001; Cohen, 1997; Ellner, 1987; Lipsitch and Samore, 2002; McEwen and Fedorka-Cray, 2002; Rubin and Samore, 2002; Vidaver, 2002). AR is a natural consequence of infectious agents' adaptation to exposure to antimicrobials used in medicine, food animals, crop production, and the widespread use of disinfectants in farm and household chores (Allen *et al*., 1999; Harris *et al*., 2002; Zaidi *et al*., 2003). The increased use of antimicrobial agents has increased selective pressure on organisms. As the opportunity for organisms to be exposed to the agents is extended, so is their opportunity to acquire mechanisms of resistance. It is now accepted that antimicrobial use is the single most important factor responsible

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for increased AR (Aarestrup, 2000, 1999; Lang *et al*., 2002; Lipsitch and Samore, 2002; Lopez-Lozano *et al*., 2000; Rubin and Samore, 2002).

Antimicrobial use is influenced by the interplay of the knowledge, expectations, and interactions of prescribers, users, and drug companies playing within the economic field and the political environment that influence the animal and public health systems and policies (Nyamogoba and Obala, 2002). While in the developed nations AR is mainly associated with overuse of the antimicrobial agents, it is paradoxical that underuse and under-dosing are the primary factors responsible for the problem in DCs (WHO, 2000). Poverty, hunger, malnutrition, coupled with other natural catastrophies in most DCs play an important role in the development and spread of AR. Unending wars and civil strife enhance the spread of the diseases of poverty such as cholera and typhoid as recently in Liberia (Moszynski, 2003) and breed good ground for development of resistance.

The recent AIDS epidemic is one single disease that has devastated societies and communities in DCs in the recent times. It has greatly enlarged the population of immunocompromised patients and left them completely defenceless and at great risk of numerous infections. Over 90% of these patients (over 30 million) are said to be found in DCs with about 22 million being found in Africa (Clark and O'Brien, 2003). This pandemic is ripping apart the social and economic fabric of this part of the world. Many AIDS patients use antimicrobial drugs more frequently to guard against or treat infections, thus increasing the selection pressure for resistant organisms. Besides, many come down with several chronic opportunistic infections, such as tuberculosis, that require hospitalisation for longer periods increasing further the risks for acquiring highly resistant pathogens found in hospital settings and spreading them (Leegaard *et al*., 2002; Phongsamart *et al*., 2002). Without making significant headway with AIDS prevention and mitigation in DCs, controlling AR will still remain an unreachable goal. This chapter discusses the current situation of AR in DCs, the factors contributing to the development and spread of the problem, the insurmountable task of controlling the problem amidst other major priorities and possible opportunities for tackling it.

2. EPIDEMIOLOGY OF ANTIMICROBIAL RESISTANCE

The epidemiology of AR is complex and influenced by many factors. Understanding the problem requires that the rates of changes in the susceptibility to specific antibiotics of organisms isolated from both man and animals be available. This enables a scientific risk assessment to be made and baselines for intervention to be established (Vose *et al*., 2001). In a bacterial population,

the three conditions responsible for the rapid spread of AR are the presence of resistance determinants, vertical or horizontal spread of these resistance determinants, and selection pressure (Edelstein, 2002; Franklin *et al*., 2002; O'Brien, 2002).

The genetic basis and the phenotypic expression of resistance is extremely complex. This is because there are different classes of antimicrobials each with a different molecular target and a single bacterial species may exhibit more than one resistance mechanism against a single class of antimicrobes (Smith and Lewin, 1993). Some bacterial species develop (or acquire) resistance more readily than others when exposed to apparently similar selective pressures (Ellner *et al*., 1987). Whether particular organisms become resistant to a particular antimicrobial agent may depend on many factors including the basic physiology of the bacteria, the characteristics of genetic mutations that occur, the prevalence of resistance genes that might be acquired, or the quantity and quality of exposure to the antimicrobial agent (Parry, 1989). For example *Escherichia coli* and enterococci (*Enterococcus faecium* and *Enterococcus faecalis*) are used internationally as Gram-negative and positive indicator bacteria, respectively, because of their ability to harbour several resistance determinants (Aarestrup, 1999; Caprioli *et al*., 2000; Catry *et al*., 2003).

Rapid spread of genes resistant to antimicrobial agents can occur in a bacterial population and from one ecosystem to another. Particular antibiotic resistance genes first described in human specific bacteria have been found in animal specific species of microorganisms and vice versa, suggesting those bacterial populations can share and exchange these genes (Aarestrup, 2000). The development of resistance in one bacterial population can, and does, spread to other populations over time.

The selection pressure determines the rate and extent of the emergence of AR. The prevalence and persistence of AR is the result of the complex interaction between antimicrobial drugs, microorganisms, the host, and the environment (O'Brien, 2002). It alters the populations through the elimination of susceptible organisms and the survival of resistant ones. The use of antimicrobials is the main cause of selection pressure(Aarestrup, 2000; Drlica, 2003; Sexton, 2000). Pathogenic organisms are clearly the target population of antimicrobial drugs, on which, by consequence a selection pressure can be exerted. Antimicrobial drugs also exert selection pressure on commensal bacteria (Blake *et al*., 2003). Commensal bacteria are present on the skin, in the upper respiratory tract, and especially in the digestive tract. The levels of AR in faecal commensal bacteria can reflect the selection pressure exerted by the use of antimicrobial agents in a certain environment (van den, 2001).

Monitoring AR gives very useful data. However, in pathogenic bacteria, it may be less accurate because the resistance patterns of pathogenic strains isolated from autopsy or following therapy failure can be altered by the

preceding antimicrobial treatment (Caprioli *et al*., 2000). Susceptibility patterns of indicator bacteria derived from healthy individuals are suggested as a good predictor of the resistance situation in the bacterial population as a whole (van den, 2001). The difference in the epidemiology of AR between the developed nations and DCs is the environmental factors especially to do with hygiene and disease control and management.

3. USE OF ANTIMICROBIAL AGENTS

The relationship between antibiotic usage and AR for many types of pathogens is largely mediated by indirect effects or population level selection (Lipsitch and Samore, 2002). When resistant and susceptible organisms compete to colonise or infect hosts, increasing use of the antibiotic will result in increase in frequency of organisms resistant to that drug in the population, even if the risk for treated patients is modest (Lipsitch and Samore, 2002). Antimicrobial use and patient to patient transmission are not independent pathways for promotion of AR, rather they are inextricably linked. Understanding in detail, for each pathogen, the mechanism by which antimicrobial use selects for AR in treated patients and in the population is of more than academic importance (Smith, 2000). For practitioners, these mechanisms matter for making well-informed decisions about the design of treatment protocols, the choice of antibiotics and doses for particular indications. For policy makers, these issues have direct bearing on the design of campaigns to encourage more rational antibiotic use and on the priorities in regulating the use of antimicrobial agents for human and animal use.

3.1. Use of antimicrobials in food animals and their impact on public health

The issue of antimicrobial use in food-producing animals has been controversial for more than three decades. Recent scientific evidence has highlighted concerns over the human health impact of resistant bacteria acquired from animals via food. Assessments examining the human health impact of antimicrobials used in food-producing animals have demonstrated quantitatively that resistance development in food-producing animals does impact on human health (Barber, 2001; Padungton and Kaneene, 2003; White *et al*., 2002).

The use of antimicrobials in veterinary practice as therapeutic and prophylactic agents in addition to use as antimicrobial growth promoters greatly influences the prevalence of resistance in animal bacteria and poses a great risk for the emergence of antibiotic resistance in human pathogens (Aarestrup,

1999; Barber, 2001). Bacterial food borne illnesses have a major public health impact and are a growing problem worldwide. Animals serve as reservoirs for many of these food borne pathogens. Epidemiological information already indicates that food of animal origin is the source of a majority of food borne bacterial infections caused by *Campylobacter, Yersinia, E. coli* 0157, non-typhoid *Salmonella*, and other pathogens (Aarestrup and Engberg, 2001; Aarestrup *et al*., 2001; Wegener *et al*., 1997). Antimicrobial use increases the frequency of AR in zoonotic pathogens (Aarestrup, 1999). Human to human transmission of zoonotic pathogens is rare, although it may occur in settings where humans are immunocompromised or where the gut community has been disturbed by heavy medical antibiotic use. Therefore, the incidence of AR in zoonotic agents of humans is directly related to the prevalence of AR bacteria in food animals (Barber *et al*., 2003; White *et al*., 2002). Antimicrobial agents have been used for many years for either treatment of infections, growth promotion in farm animals, or for prophylactic use in intensive animal rearing. The worldwide use of antibiotics for animal health purposes was estimated at 27,000 tonnes of which 25% was used in Europe (Degener, 2002). Table 1 shows a comparison between the use of antimicrobial agents between a DC (Kenya) and a developed nation ranked as a low ratio user (Denmark). Clearly there is more use of antibiotics in Denmark than Kenya.

The use of antimicrobials in food-producing animals can lead to emergence of resistant bacterial strains, allergic reactions in animals and humans, and other adverse effects depending on the compound (Aarestrup *et al*., 2001; Tollefson and Flynn, 2002). Bacteria from animals may reach the human population by many routes. Drug-resistant bacteria of animal origin, such as *E. coli* and *Enterococcus* spp. can colonise the intestine of humans (Wegener *et al*., 1997). Heavily exposed individuals like slaughterhouse workers, food handlers, and farmers feeding antimicrobials to animals have a higher frequency

Table 1. Comparison of consumption of antibiotics (kg) in food animals between a developing country (Kenya) and a developed nation (in brackets, Denmark)

Antimicrobial class	Year		
	1996	1998	1999
Tetracycline	15,889 (12,900)	7,782 (12,100)	3,324 (16,200)
β-lactams	572 (13,000)	1,921 (21000)	1195 (21,300)
Aminoglycosides	752 (7,100)	2,421 (7,800)	843 (7,500)
Macrolides	165 (7,600)	8 (7100)	000 (8,700)
Sulfonamides	499 (2,100)	934 (100)	6,604 (100)
Quinolones	8 (NA)	177 (400)	252 (150)

Sources: Mitema *et al*. (2001), Anonymous (1999), NA—Not available.

of resistant organisms. Besides transfer of drug resistance there is another important problem of drug residues in animal products at slaughter. While this problem has been addressed in developed nations by defining Maximum Residue Levels (MRL) for most drugs for the maximum acceptable level of antibiotics in animal products, very little information is available in DCs and there is almost nothing done to enforce some of these international standards. Only isolated studies have been done to collect data on which rational decisions for intervention can be based.

4. THREAT OF ANTIMICROBIAL RESISTANCE

Antimicrobial resistance is a natural biological phenomenon. It has become a significant public health problem because it has been amplified many times as a natural consequence of bacterial adaptation to exposure to antimicrobials used in medicine, food animals, crop production, and the widespread use of disinfectants in farm and household products (Bloomfield, 2002; McEwen and Ferdorka-Cray, 2002; Vidaver, 2002). There is an increasing decline in effectiveness of the existing antimicrobial agents. Infections have thus become more difficult and expensive to treat and epidemics harder to control (Cohen, 1994). While the use of drugs combined with improvements in sanitation, housing, and nutrition, and the advent of wide-spread immunisation programmes have led to a dramatic drop in deaths from diseases that were previously widespread, untreatable, and frequently fatal in developed nations. The situation in DCs remains as grim or worse than that of the previous generations of the industrialised nations. Preventable infectious diseases are still present, threatening the life and people's livelihoods, causing deaths and suffering of the underprivileged populations due to poverty, hunger, and inadequate resources. Previously treatable infectious diseases such as tuberculosis, malaria, acute respiratory diseases, and diarrhoea now cause the highest morbidity and mortality in DCs. Table 2 shows examples of some of the most important pathogens in DCs in which the resistance problem has developed.

4.1. Resistance in malaria

Malaria is one of the most serious public health problems and a leading cause of morbidity and mortality in many tropical countries. Malaria kills more than 1 million people a year, and 3,000 deaths a day (WHO, 2002). Hundreds of millions of people most of them children and pregnant women in sub-Saharan Africa suffer acute attacks of malaria-induced fever, often several times a year. It is a complex disease that varies widely in epidemiology and clinical manifestation in different parts of the world. This variability is the result of factors such

Table 2. Resistance to important bacterial pathogens in developing countries

Disease	Agent	Resistance
Malaria	*Plasmodium falciparum*	Chloroquine
Pneumonia	*Streptococcus pneumoniae*	Penicillin
Dysentery	*Shigella dysenteriae*	Multiresistant
Typhoid	*Salmonella typhi*	Multiresistant
Gonorrhoea	*Neisseria gonorrhoeae*	Pen and tetracycline
Tuberculosis	*Mycobacterium tuberculosis*	Rifampicin and INH
HIV/AIDS	HIV-1 non-B subtype	NRTIs, PIs, and NNRTIs
Nosocomial	*Staphylococcus aureus*	Methicillin resistant.

Notes: NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; Pen, penicillin; PI, protease inhibitor; INH, isoniazid.

as the species of malaria parasites that occur in a given area, their susceptibility to commonly used or available anti-malarial drugs, the distribution and efficiency of mosquito vectors, climate and other environmental conditions, and the behaviour and level of acquired immunity of the exposed human populations. Drug resistance has been implicated in the spread of malaria to new areas and re-emergence of malaria in areas where the disease had been eradicated (Bloland, 1993). Drug resistance also plays a significant role in the occurrence and severity of epidemics in some parts of the world. Population movement has introduced resistant parasites to areas previously free of drug resistance. The economics of developing new pharmaceuticals for tropical diseases, including malaria, are such that there is a great disparity between the public health importance of the disease and the amount of resources invested in developing new cures (Ridley, 1997). This disparity comes at a time when malaria parasites have demonstrated resistance to almost every anti-malarial drug currently available, significantly increasing the cost and complexity of achieving parasitological cure.

For decades chloroquine (CQ) was the mainstay of anti-malarial therapy but the emergence of *Plasmodium falciparum* resistance has challenged the control efforts (Campbell, 1991). In East Africa, the level of resistance has risen steadily over the last 20 years, with recent studies indicating that CQ fails to clear parasites in upto 50–80% of patients (Bayouni *et al*., 1989; Branding-Bennett *et al*., 1988; Fowler *et al*., 1993; Premji *et al*., 1993; Watkins *et al*., 1988; Wolday *et al*., 1995). Table 3 shows clinical failure rates for CQ and sulfadoxine-pyrimethamine (SP) in Uganda.

Despite these rising levels of resistance, CQ has remained the first-line anti-malarial in many African countries because of its low cost and observed clinical efficacy (Barat, 1998; Hoffman *et al*., 1998). The spread of CQ resistance has been temporarily associated with increased malaria-related morbidity and

Table 3. *In vivo* clinical failure rates of *P. falciparum* to chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) in Uganda (1996–9) in children under <5 years, during 14 days of follow up

District	Year	Geographic location	Clinical failure rates			
			CQ		SP	
			n	%	*n*	%
Bundibugyo	1996	Rural	60	33	38	5
Kabarole	1996	Road side	60	58	29	3
Jinja	1996	Urban	52	12	35	7
Tororo	1996	Road side	33	60	—	—
Tororo	1997	Rural	78	22	—	—
Mbarara	1997	Hospital	53	81	64	25
Kampala	1998–9	Urban	142	62	45	11

Sources: Kamya *et al*., 2002, Kilian *et al*. (1997).

mortality in Africa, highlighting the urgent need to change anti-malarial drug policy (Trape, 2001) in some countries (Kamya *et al*., 2002). Because of the current healthcare infrastructure and the influence of the private sector, approaches to malaria therapy in sub-Saharan Africa will favour increased access to drugs over restricted access which may lead to short-term reductions in malaria morbidity and mortality but is also likely to further increase resistance. Mathematical models for the transmission dynamics of drug sensitive and resistant strains have been developed and can be a useful tool to help to understand the factors that influence the spread of drug resistance and can therefore help in the design of rational strategies for the control of drug resistance (Koella and Antia, 2003). However, significant advances against anti-malarial drug resistance is probably unlikely to be achieved without major improvements in health infrastructure leading to higher quality services that are more readily available.

4.2. Resistance in tuberculosis

Tuberculosis is an enormous global health problem. The burden of the disease in DCs continues to grow largely fuelled by the HIV/AIDS pandemic and poor public health infrastructure (Yun *et al*., 2003). The incidence of tuberculosis in Africa is estimated at 259 persons per 100,000 population per year compared to about 50 per 100,000 population per year in Europe and America (Dye *et al*., 1999). Resistance of *Mycobacterium tuberculosis* to antibiotics is a man-made amplification of spontaneous mutations in the genes of the tubercle bacilli. Treatment with a single drug due to irregular drug supply,

inappropriate prescription, or poor adherence to treatment suppresses the growth of susceptible strains to that drug but permits the multiplication of drug-resistant strains. Dramatic outbreaks of multidrug-resistant tuberculosis (MDR-TB) in HIV-infected patients have recently focused international attention on the emergence of strains of *M. tuberculosis* resistant to antimycobacterial drugs (Yun *et al*., 2003). MDR-TB, defined as resistance to the two most important drugs, isoniazid (INH) and rifampicin (RMP) is a real threat to tuberculosis control. The prevalence of drug resistance, including MDR in different countries, has been extensively reviewed by WHO (1997) and a comparison between some developed nations and DCs is given in Table 4.

The prevalence of primary resistance to any drug ranged from 2% to 41%. Primary MDR-TB was found in every country surveyed except Kenya (surprisingly) (WHO, 1997). The prevalence of acquired drug resistance ranged from 5.3% to 100% and was much higher than that of primary drug resistance. Patients infected with strains resistant to multiple drugs are extremely difficult to cure, and the necessary treatment is much more toxic and expensive. Drug resistance is therefore a potential threat to the standard international method of TB control: the DOTS strategy ("Directly Observed

Table 4. Comparison of prevalence of anti-tuberculosis primary drug resistance between developed nations and DCs (acquired drug resistance figures shown in brackets)

Country	Patients tested	Overall resistance (%)	Resistance to 1 drug (%)	MDR (%)
USA	13,511 (833)	12.3 (23.6)	8.2 (12.5)	1.6 (7.1)
England	2,742 (148)	6.9 (32.4)	4.6 (12.2)	1.1 (16.9)
France	1,491 (195)	8.2 (21.5)	5.6 (12.3)	0.5 (4.1)
Brazil	2,095 (793)	8.6 (14.4)	6.4 (7.3)	0.9 (5.4)
Argentina	606 (288)	12.5 (41.3)	6.6 (12.2)	4.6 (22.2)
Swaziland	334 (44)	11.7 (20.5)	6.6 (9.1)	0.9 (9.1)
Zimbabwe	676 (36)	3.3 (13.9)	1.3 (5.6)	1.9 (8.3)
Botswana	407 (114)	3.7 (14.9)	3.4 (7.0)	0.2 (6.1)
Lesotho	330 (53)	8.8 (34.0)	6.1 (20.8)	0.9 (5.7)
SierraLeone	463 (172)	28.1 (52.9)	16.6 (16.3)	1.1 (12.8)
Kenya	445 (46)	6.3 (37.0)	5.4 (30.4)	0.0 (0.0)

Definitions: Primary resistance is the presence of resistant strains of *M. tuberculosis* in a patient with no history of such prior treatment. Acquired resistance is that which is found in a patient who has received at least 1 month of prior anti-tuberculosis drug treatment. Multidrug resistance (MDR) is defined as resistance to at least INH and RMP, the two most potent drugs and the mainstay of anti-tuberculosis treatment. Overall resistance refers to the proportion of isolates that are resistant to one or more drugs in either primary or acquired resistance.

Source: WHO, 1997.

Treatment, Short-course"). Although preventive therapy decreases the risk of developing active tuberculosis in HIV-infected persons, only a few studies have reported decrease in mortality (Pape *et al*., 1993). While the availability of effective short-course treatment has been beneficial, tuberculosis still remains one of the greatest global health problems. The number of tuberculosis cases continues to increase in sub-Saharan Africa in contrast to decreasing numbers of cases in developed nations (Johnson and Ellner, 2000). This is principally due to poverty, civil strife, economic turmoil, and bad governance. In DCs, the majority of deaths are not due to MDR-TB but rather due to lack of effective and rationally delivered therapy for drug susceptible tuberculosis.

4.3. Resistance in HIV/AIDS

The AIDS epidemic is one single disease that has devastated societies and communities in DCs in the recent times. It has greatly enlarged the population of immunocompromised patients and left them completely defenceless and at great risk of numerous infections. About 22 million people around the world have died from AIDS, and about 40 million more are currently infected with the HIV virus (Clark and O'Brien, 2003). About 83% of AIDS deaths and 71% of HIV infections have occurred in war-ravaged, poverty-stricken DCs in sub-Saharan Africa (Mason and Katzenstein, 2000). This pandemic is ripping apart the social and economic fabric of this part of the world. Only by giving those infected with HIV effective treatments, will people be prevented from dying of AIDS in the future.

Many AIDS patients use antimicrobial drugs more frequently to guard against or treat infections, thus increasing the selection pressure for resistant organisms (Tumbarello *et al*., 2002; Zar *et al*., 2003). Besides, many contract several chronic opportunistic infections, such as tuberculosis, that require hospitalisation for longer periods increasing further the risks for acquiring highly resistant pathogens found in hospital settings and spreading them (Yun *et al*., 2003). Despite the fact that many of the anti-retroviral (ARV) drugs are simply unaffordable to many patients in many DCs, resistance has been reported. Most patients receive cheaper, lower cost drugs instead of highly active anti-retroviral therapy (HAART) which is more effective but more expensive and unaffordable to many. Although they may get some beneficial response more drug resistance has been found in these patients, especially against lamivudine, than those on HAART (Weidle *et al*., 2002). Resistance to at least one drug has been reported in 61% of patients studied in Uganda even in patients who had never received treatment (Weidle *et al*., 2002) implying infection with resistant virus. The high cost of ARV drugs is a very high risk to development of resistance in poor resource countries.

4.4. Resistance in respiratory infections

Acute respiratory infections (ARI) are a leading cause of childhood mortality, causing 25–33% of all deaths in children in DCs (Berman, 1991). Bacterial ARI are associated with higher case-fatality ratios than infections caused by viruses. *Streptococcus pneumoniae* is the most common cause of bacterial ARI (Huerbner *et al*., 2000; Kristinsson, 1997). ARI are often treated empirically with antibiotics. Drug-resistance trends are not well documented in most DCs due to limited laboratory capacity (O'Dempse *et al*., 1996; Forgie, 1992). It is clear, however, that the prevalence of strains resistant to penicillin-related compounds and to co-trimoxazole is increasing (Appellbaum, 1992).

Epidemiological studies have demonstrated that recent antibiotic use is strongly associated with carriage of resistant pneumococci both at the community and individual levels. Among individuals who develop invasive pneumococcal disease, recent antibiotic use poses an increased risk of infection with a resistant strain (Kristinsson, 1997). The biological mechanisms behind the association between recent antibiotic use and carriage of resistant strains are not completely understood. A key factor influencing the emergence and spread of resistant pneumococci is unnecessary antibiotic use for viral respiratory illnesses in humans. This is due to misdiagnosis of conditions because both viral and bacterial agents can cause symptoms of ARI, as well as physician and patient pressures to prescribe antibiotics.

However, while antibiotic overuse is a problem in some developing nations, in DCs, poor access to adequate healthcare is still a primary problem and children requiring antibiotic therapy do not receive it (Berman, 1991).

4.5. Resistance in enteric bacteria

Important enteric pathogens are becoming increasingly resistant to the major antibiotics that are needed for optimal treatment of patients. Some of the important pathogens include *Vibrio cholerae, Shigella* spp, *Salmonella* spp, and *Campylobacter jejuni* (Hofer *et al*., 1999; Kariuki, 2001). They cause quite different clinical syndromes; their ecology, epidemiology, and modes of transmission are distinct; and they are widely separated genetically. The fact that these different organisms are becoming increasingly antibiotic-resistant underlines the pervasiveness of the pressures that lead to the emergence and spread of resistance. The prevalence of one of them, *Salmonella typhi* in Egypt is summarised in Table 5.

In DCs, laboratory services, appropriate transport of specimens, and access to healthcare services remain problematic (Hofer *et al*., 1999; Keusch, 1988).

Table 5. Prevalence of drug resistance to *Salmonella typhi* in Egypt over a 5-year period (1988–1992)

Year	Percent resistance (Number of isolates in brackets)					
	Amp	Chl	TMP-SMX	EM	Tet	MDR
1988	24 (58)	25 (28)	24 (28)	75 (2)	11 (28)	24 (60)
1989	45 (51)	30 (10)	45 (38)	69 (51)	41 (41)	45 (51)
1990	65 (48)	59 (48)	29 (48)	92 (48)	NA	60 (48)
1991	65 (114)	61 (93)	55 (111)	90 (93)	56 (111)	61 (127)
1992	66 (114)	28 (114)	53 (114)	100 (110)	49 (114)	53 (114)

Notes: Amp—Ampicillin; Chl—Chloramphenicol; TMP-SMX—Trimethoprim-Sulfamethoxazole; EM—Erythromycin; Tet—Tetracycline; MDR—Multidrug resistance; NA—Not available.

Source: Wasfy *et al*. (2002).

Data may be subject to bias, as information often comes from hospital-based surveillance and therefore may reflect the more severe infections. Similarly, the data from epidemics may not reflect the situation during non-epidemic periods.

4.6. Resistance in nosocomial infections

Drug resistance in hospital-acquired infections poses serious constraints on the options available for treatment (Jones, 1992; Kariuki *et al*., 1993). Nosocomial infections caused by bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) pose a serious therapeutic problem worldwide (Pulimood *et al*., 1996), although information on its frequency in most African countries is not available (Kesah *et al*., 2003). MRSA is a well-known etiologic agent of very serious infections and more so in HIV-infected patients (Tumbarello *et al*., 2002). The endemicity of this pathogen in many countries today and the resistance of such isolates to most anti-staphylococcal antibiotics represent a grave threat to public health. In Africa, data on MRSA, particularly antibiotic susceptibilities, are extremely limited. Table 6 shows available data on the prevalence of MRSA in some DCs. The rate of MRSA is relatively high in Nigeria, Kenya, and Cameroon (21–30%), and below 10% in Tunisia and Algeria. All MRSA isolates were sensitive to vancomycin, with MICs $\leq$ 4 mg/L (Kesah *et al*., 2003). While the resistance levels may not be so worrying, there is a need to maintain surveillance and control of MRSA infections in Africa where alternative treatment may not be readily available or affordable.

Table 6. Prevalence of MRSA in sub-Saharan Africa 1996–7

Country	Total number of isolates	Number of MRSA	% Resistance
Cote D'Ivore	155	26	16.8
Morocco	167	24	14.4
Tunisia	186	15	8.1
Algeria	208	10	6.7
Senegal	168	21	12.5
Nigeria	142	42	29.6
Cameroon	127	27	21.3
Kenya	137	38	27.7

Source: Kesah *et al*. (2003).

4.7. Resistance in animal diseases

In human medicine, AR and especially the multiple resistance of *S. aureus*, pneumococci, enterococci, and *Enterobacteriaceae* isolated both from nosocomial and non-hospital-related infections (Schwartz *et al*., 2001) have been found to cause therapy failure and higher morbidity and mortality rates. Major economic losses and animal welfare problems could arise in veterinary medicine, as well, if AR evolves towards a comparable critical level. Resistance of animal pathogens in veterinary medicine are already alarming and are comparable to the situation in humans in DCs. Table 7 shows resistance patterns of clinical isolates from bovine mastitis in Uganda. While the data from clinical isolates may be biased because of previous antibiotic therapy, they nevertheless give an indication of the extent of the problem.

It is now generally accepted that AR in veterinary medicine forms a potential public health hazard. Indeed, the commensal gastrointestinal flora of healthy animals are a reservoir of resistance genes (van den, 2000) that can colonise the flora of humans through the food chain or by direct contact. If, moreover, the underlying resistance genes are horizontally transferred into human pathogenic bacteria, this can result in treatment failure as a consequence of AR (Wegener *et al*., 1997). The importance of this indirect path of resistance transfer is less clear than for the direct transfer of resistant zoonotic organisms. Because livestock animals are carriers of food-borne pathogens such as *Salmonella* and *Campylobacter* spp, these species also undergo similar selection pressure due to the use of antimicrobial drugs (Aarestrup and Engberg, 2001). As a result, treatment failure in humans arises as a consequence of the intake of these selected resistant organisms either through the food chain and/or through direct contact (Kruse, 1999), irrespective of the horizontal transfer of resistance genes.

Table 7. Resistance patterns of bacteria isolates from bovine clinical mastitis in Uganda

Antibiotic	Per cent resistance to clinically important isolates					
	S. aureus	*Strepto-coccus* spp	*E. coli*	*Klebsiella* spp	*Pseudomonas aeruginosa*	*Coryne-bacterium pyogenes*
Gentamicin	26	0	9	21	30	0
Kanamycin	19	0	22	22	70	0
Chloramphenicol	23	21	35	32	80	20
Erythromycin	47	41	62	8	92	60
Neomycin	43	51	42	3	NA	NA
Streptomycin	39	40	63	66	90	100
Tetracycline	100	100	100	67	70	80
Cloxacillin	96	90	100	100	100	100
Ampicillin	100	76	100	100	97	60
Penicillin	95	90	NA	NA	NA	NA

Source: Byarugaba *et al*. (2001).

5. IMPLICATIONS OF HIV/AIDS ON THE ANTIMICROBIAL RESISTANCE PROBLEM

Many AIDS patients use antimicrobial drugs more frequently to guard against or treat infections, thus increasing the selection pressure for resistant organisms (Badri *et al*., 2001). Besides, many come down with several chronic opportunistic infections, such as tuberculosis, that require hospitalisation for longer periods, increasing further the risks for acquiring highly resistant pathogens found in hospital settings and spreading them (Leegaard *et al*., 2002). The impact of HIV/AIDS depends on the dual infection with other secondary infections such as tuberculosis, meningitis, pneumonia, and other infections (Leegaard *et al*., 2002; Phongsamart *et al*., 2002). HIV-infected individuals are at least 30-fold more likely to develop reactivation tuberculosis as HIV infection progresses and are more susceptible to exogenous re-infection and rapid progression to active tuberculosis when re-infected with *M. tuberculosis* (Puerto Alonso *et al*., 2002).

The interaction of tuberculosis and HIV/AIDS is complex (Phongsamart *et al*., 2002; Puerto Alonso *et al*., 2002). The addition of several medications for treatment of tuberculosis for HIV patients already on ARV drugs makes adherence sometimes difficult. Complications often make it worse. These are important risk factors to development of resistance. Implementing and sustaining preventive therapy in HIV-infected persons in Africa bears formidable challenges that require comprehensive efforts for counselling, monitoring of

side effects, and supervision of treatment (Mason and Katzenstein, 2000). Given the lack of good infrastructure in most DCs this becomes even more difficult.

The increased use of antibiotics in HIV/AIDS infected persons due to their immunocompromised status breeds good ground for development of AR (Tumbarello *et al*., 2002). Studies have been published on the use of trimethoprim-sulfamethoxazole (TMP-SMX) (co-trimoxazole) for prophylaxis in HIV/AIDS patients (Badri *et al*., 2001). In developed countries it is used for prophylaxis against *Pneumocystis carinii* pneumonia in HIV-infected individuals but has gained importance in Africa as well for prophylaxis against other infections such as toxoplasmosis, isosporiasis, *S. pneumonia*, and non-typhi *Salmonella* species which are frequent causes of morbidity and mortality in HIV-infected Africans. In DCs where ARV drugs are not affordable this prophylaxis, because of its low cost, may benefit the HIV-infected patients and has been reported to decrease septicaemia and enteritis significantly (Mason and Katzenstein, 2000). However there is also a danger of developing resistance to this drug as has been reported for many isolates, thus further compromising the benefits of these prophylaxis strategies (Zar *et al*., 2003).

Evidence from prevention of malaria during pregnancy suggests that parasitological response to treatment among individuals infected with the HIV may also be poor. HIV-seropositive women require more frequent treatment with SP (sulfadoxine-pyrimethamine) during pregnancy in order to have the same risk of placental malaria as is seen among HIV-seronegative women (Parise *et al*., 1998). Parasitological response to treatment of acute malaria among HIV-seropositive individuals has not been evaluated though.

6. ECONOMIC IMPLICATIONS OF ANTIMICROBIAL RESISTANCE

Antimicrobial resistance is not only a medical problem but also an economic one (Paladino *et al*., 2002). Resistant organisms cause infections that are more difficult to treat, requiring drugs that are often less readily available, more expensive, and more toxic (Carmeli *et al*., 1999; Howard *et al*., 2001). In some cases, certain strains of microbes have become resistant to all available antimicrobial agents (Russo and Johnson, 2003). Resistant Gram-negative and Gram-positive bacteria have been associated with increased direct medical costs ranging from several thousand dollars to tens of thousands of dollars per patient (Paladino *et al*., 2002). With increasing frequency and levels of AR, drug therapy must be viewed in an economic sense. Several factors impact on cost-effective antimicrobial therapy, including drug cost, drug efficacy and

duration of treatment, dose regimen, diagnostic strategies, microbial resistance, and patient compliance.

Comparison has been made of the impacts of infections due to antimicrobial-resistant bacteria with those of infections due to antimicrobial-susceptible strains of the same bacteria. Data shows that for both nosocomial and community-acquired infections, the mortality, the likelihood of hospitalisation and the length of hospital stay were usually at least twice as great for patients infected with drug-resistant strains as for those infected with drug-susceptible strains of the same bacteria (Holmberg *et al*., 1987). Tuberculosis, treatment costs have been estimated at US$20 for regular treatment, while the cost of treating MDR-TB rises to US$2,000 (WHO, 2001). For HIV/AIDS, it has been indicated that resistance to one protease inhibitor results in resistance to the entire family of drugs thus implying higher costs of treatment of the insensitive strains. This applies to all other major killers such as ARIs, diarrhoeal diseases, malaria, and other STDs which are very prevalent in DCs. Poor outcomes could be attributed both to the expected effects of ineffective antimicrobial therapy and to the unexpected occurrence of drug-resistant infections complicated by prior antimicrobial therapy for other medical problems. Although the adverse economic and health effects of drug-resistant bacterial infections can only be roughly quantified, AR is an important health problem and an economic burden to society (Cosgrove and Carmeli, 2003).

Unfortunately the costs for production of new drugs and introduction onto the market are enormous, estimated at a minimum of US$300 million. This partly explains the reason why since 1970, there have been few classes of antimicrobial agents developed. Their development also takes a period of 10–20 years. Although DCs have the enormous potential of hotspot virgin tropical forests that harbour a lot of plant resources that may provide solutions to many of the current resistance problems, their exploitation requires similar huge financial resources and time to develop them to market level.

Besides the direct costs, there are also biological costs associated with development of AR (Gillespie and McHugh, 1997; Nyamogoba and Obala, 2002) and more importantly, costs related to loss of life and hours spent without productive work during long hospitalisation with resistant disease agents. Table 8 shows the extent of the deaths resulting from major killer diseases in the DCs.

Together, HIV/AIDS, tuberculosis, and malaria claimed 5.7 million lives in 2002 and caused debilitating illness in many millions more (Goeman *et al*., 1991; WHO, 2002). These are the lives of infants, young children, and young mothers and fathers and the economically most important group in their prime productive years. Resistance to these disease agents puts a heavy burden on the already strained public health.

Table 8. Occurrence of the major killer diseases in the world and proportion of their occurrence in developing countries

Disease	Deaths per year (in million)	New cases per year (in million)	Percentage in developing countries (%)
HIV/AIDS	3	5.3	92
Tuberculosis	1.9	8.8	84
Malaria	>1	300	Nearly 100

Source: WHO (2002).

7. FACTORS CONTRIBUTING TO DEVELOPMENT AND SPREAD OF RESISTANCE

The development and spread of AR is a complex problem driven by numerous interconnected factors, many of which are linked to the use of antimicrobials both in animals, plants and man. It is now accepted that antimicrobial use is the single most important factor responsible for increased AR (McGarock, 2002; Mitema *et al*., 2001; Rubin and Samore, 2002). Antimicrobial use is influenced by interplay of the knowledge, expectations and interactions of prescribers and patients, economic incentives, characteristics of the health systems, the regulatory environment, and availability of resources. Organisms themselves possess characteristics that enable them to be resistant and these may be enhanced by other environmental factors (Allen *et al*., 1999; Harris *et al*., 2002; Tumbarello *et al*., 2000; Zaidi *et al*., 2003). Thus extreme poverty in most DCs leads to poor sanitation, hunger, starvation and malnutrition, poor access to drugs, and poor healthcare delivery, all of which may precipitate AR.

7.1. Poverty

Most DCs have inadequate healthcare systems due to limited resources. A health sector situational analysis in Uganda, one of the poorest countries, indicated that with a population of 26 million and a growth rate of 2.5% and fertility rate of 6.9, 49% of this population live below the poverty line, surviving on less than $1 per day. According to disease burden studies, 75% of the life years of Ugandans are lost to premature death due to preventable diseases with malaria being responsible for 15.4%, acute respiratory tract infections 10.5% and diarrhoea 8.4%. HIV/AIDS also, still, claims thousands of lives despite the significant decreases in the prevalence rates in the country. The geographical access to healthcare is limited to about 49% of the population,

that is, population living within 5 km of a health unit (Health Facilities Inventory, 1992). Rural communities are particularly affected because health facilities are mostly located in towns and along main roads. Even among these facilities, many do not provide the full range of essential primary healthcare services. This poor health status prevails in most DCs and AR is seen as a secondary problem and not an immediate priority.

7.2. Malnutrition and hunger

The current prevalence of malnutrition among African children under 5 years has been estimated to be 30% and an estimated 4–5 million children were thought to be infected with HIV at the beginning of this century (Brabin *et al*., 2001; WHO, 2002). Among refugee children in the former Zaire, those who were malnourished (low weight for height) had significantly poorer parasitological response to both CQ and SP treatment (Wolday *et al*., 1995). If it is proven that malnutrition or HIV infection plays a significant role in facilitating the development or intensification of anti-malarial drug resistance, the prevalence of these illnesses could pose a tremendous threat to existing and future anti-malarial drugs. Some characteristics of recrudescent or drug resistant infections appear to provide a survival advantage or to facilitate the spread of resistance conferring genes in a population which is further aggravated by low nutritional and immune status.

7.3. Civil wars and unrest

Civil wars in many DCs have been responsible for breakdown of many health services and have forced many people into refugee camps, or internally displaced people camps. In such concentration camps there is often very poor hygiene and sanitation, good ground for spread of infection, and high selection and spread of resistant organisms. The perpetual wars also limit the enforcement of laws governing manufacture, market authorisation, distribution, and monitoring the sale of drugs, thus predisposing the population to poor and counterfeit drugs.

7.4. Natural catastrophies

Climatic and weather patterns influence the occurrence, incidence, and distribution of infectious diseases such as cholera and malaria (Shears, 2001). Heavy rains and floods overwhelm the already dilapidated drainage systems, spreading organisms, some of them very resistant, while dry weather encourages spread of airborne pathogens (Byarugaba *et al*., 2001).

7.5. Human population growth

The fast growth of globalisation accompanied by enormous growth of trade and travel has increased the speed and facility with which both infectious diseases and resistant microorganisms can spread between continents. The ability of DCs to cope with this globalisation and the attendant spread of resistant organisms all over the world is severely stretched (WHO, 2000). The increased growth has also meant increased demand for resources and services. The rapid population increases and urbanisation without corresponding increase in resources and services has resulted in overcrowding and poor hygiene and sanitation which greatly facilitate the spread of such diseases as typhoid, tuberculosis, respiratory infections, and pneumonia.

7.6. Societal factors

Societal factors are one of the major drivers of inappropriate antimicrobial use. These include self-medication, non-compliance, misinformation, poor immune status, wrong conceptions and beliefs, advertising pressures, and treatment expectations (Byarugaba *et al*., 2001; Lipsitch and Samore, 2002; Parimi *et al*., 2002). The most important underlying factor in DCs, however, is poverty (Hossain *et al*., 1982). Lack of resources, compounds with other factors as it relates to ignorance, lack of purchasing power, lack of education, and lack of access to proper health facilities and diagnostic facilities (Lindtjorn, 1987). Poverty also means people do not get sufficient food to keep their bodies healthy and fit to fight off infections. They live in poor hygiene, are exposed to water-borne infections due to drinking contaminated water which exposes them to diseases of poverty, such as cholera, typhoid, and other infections. Often economic hardships in DCs lead to premature cessation of treatment or sharing of a single treatment course by a whole family (Byarugaba *et al*., 2001).

7.7. Service providers

In many DCs healthcare providers are influenced by financial gains from their practice as they are operated on cost–benefit basis (Byarugaba *et al*., 2001; Indalo, 1997). This financial interest makes them prescribe antimicrobials even when they are not clinically indicated. Additional profit is sometimes gained by recommending newer and more expensive antimicrobials in preference to older cheaper agents and combination therapies where it is uncalled for, such as in malaria (Anakbonggo and Birungi, 1997). Pharmaceutical companies have been known to pay commissions to prescribers who use more of their products. Besides, the aggressive advertisement methods of many drug

companies in electronic and print media leave the prescribers and dispensers vulnerable and the laws regarding such advertising are never implemented due to lack of commitment and resources on the part of the law enforcement departments (Lipsky, 1997). Other factors relating to healthcare providers include, lack of proper training, unprofessional conduct, lack of diagnostic facilities, wrong selection of antimicrobial agents, patient pressures for specific antimicrobials, and fear of treatment failure (Byarugaba *et al*., 2001).

7.8. Health institutions

Hospitals are a critical component of the AR problem worldwide (Allen *et al*., 1999; Goldmann *et al*., 1996; Harris *et al*., 2002; Tumbarello *et al*., 2002; Zaidi *et al*., 2003). The combination of highly susceptible patients, intensive and prolonged antimicrobial use and cross-infection have resulted in highly resistant bacterial pathogens. Many of the health facilities are overcrowded and have limited capacity compared to the inflow of patients, as they were built many years ago for a smaller population.

Hospitals are also the eventual site of treatment for many patients with severe infections due to resistant pathogens acquired in the community. Recent introduction of free medical care to the population in Uganda saw most health-care units flooded with patients, completely overwhelming the wards. Other small health centers and clinics encounter similar problems. The situation is even worse for those located in rural settings far away from town centers where drug supplies are limited and laboratory facilities are unavailable (Byarugaba *et al*., 2001).

7.9. Policies

Globalisation has come with many structural adjustments to keep pace with developments in the rest of the world. The underlying principles of many national drug policies aim to contribute to the attainment of good standards of health by the population, through ensuring the availability, accessibility, and affordability, at all times, of essential drugs of appropriate quality, safety, and efficacy, and by promoting their rational use. However, many of these laws only exist on paper or are poorly communicated to the stakeholders and thus implementation is still difficult due to gross under funding of the health sector. Besides, some result out of inadequate consultation.

Structural adjustment programmes originating from development partners have also had an impact on healthcare delivery systems. Under the current decentralisation in many DCs, districts have the obligation to deliver a package of health services to the population, while the ministries only provide them

with the technical support and supervision. Many of the districts do not have sufficient resources and personnel to implement some of the policies and to provide adequate health services. The policies of privatisation and liberalisation have also affected the procurement and supply of drugs. With inadequate supervision from regulatory agencies, these have resulted in sale of expired and counterfeit drugs (Byarugaba *et al*, 2001).

7.10. Use of antimicrobial drugs in food animal production

As already mentioned in Section 3.1, the use of antimicrobials in veterinary practice as therapeutic and prophylactic agents in addition to use as antimicrobial growth promoters greatly influences the prevalence of resistance in animal bacteria and poses a great risk for the emergence of antibiotic resistance in human pathogens (Barber, 2001; McDermott *et al*., 2002; Shah *et al*., 1993). There is already high resistance against many antibiotics in livestock (Catry *et al*., 2003b). The extent to which antibiotic use in animals contributes to the AR in humans is still under debate. However, a wealth of epidemiological information already indicates that food of animal origin is the source of a majority of food borne bacterial infections caused by *Campylobacter, Yersinia, E. coli* (Schroeder *et al*., 2002a, b), non-typhoid *Salmonella* (Angulo *et al*., 2000), and other pathogens. Direct evidence indicates that antimicrobial use in animals selects for antimicrobial-resistant bacteria that may be transferred to humans through food or direct contact with animals (Aarestrup, 1999; Aarestrup *et al*., 2001). In DCs the deliberate use of antimicrobial drugs as growth promoters is still on a limited scale. However, many antimicrobial drugs are used in animals for prophylaxis and therapy (Nakavuma *et al*., 1994; Mitema *et al*., 2001). Several guidelines are available for appropriate use of drugs in animals (Anthony *et al*., 2001; Nicholls *et al*., 2001), but very little is being done in DCs.

8. STRATEGIES FOR CONTAINMENT OF RESISTANCE IN DEVELOPING COUNTRIES

The problem of AR is a global one and will require a concerted effort and cooperation among nations. Several suggestions have been made (Burke, 2002; Coast and Smith, 2003; Kettler, 2000; Schwartz *et al*., 1997; Lees and Shojaee, 2002; Wise, 2002) although there is absence of good published evidence concerning cost-effectiveness in reducing emerging resistance (Wilton *et al*., 2002). Containment will depend on coordinated interventions that simultaneously

target the behaviour of providers and patients, and change important features of the environment in which they interact, as well as managerial and policy issues which have been well articulated (Barrett, 2000; Dagan *et al*., 2001; de Man *et al*., 2000; Gruson *et al*., 2000; Hooton and Levy, 2001; Murthy, 2001; Poole, 2001; Samaranayake and Johnson, 1999; Schwartz *et al*., 1997; Schwarz *et al*., 2001; Sehgal, 1999; Semjen, 2000; Sirinavin *et al*., 1998; Slots, 1999; Smith, 1999; Tan *et al*., 2002; Weinstein, 2001; Wise, 2002).

However, responsible use of the available antimicrobial agents is of paramount importance despite the challenges DCs face (Byarugaba *et al*., 2003). Use of antimicrobial agents in food producing animals should follow prudent principles to minimise the selection and spread of resistant zoonotic bacteria like *Salmonella* spp and *Campylobacter* spp. Emphasis should be placed on disease preventive measures such as good farm management and hygiene to reduce bacterial load, rather than use of antimicrobials (WHO, 2000). The goal of any programme to monitor the quantities of antimicrobials used in animals is to generate objective quantitative information to evaluate usage patterns by animal species, antimicrobial class, and type of use. These data are essential for risk analysis and planning and can be helpful in interpreting resistance surveillance data and evaluating the effectiveness of prudent use efforts and mitigation strategies. The total consumption of antimicrobials for human usage, food animal, and other uses is a key factor in any consideration of this issue. Data on antimicrobial consumption is scanty and has been reported in only a few countries (Anonymous, 1999; Grave, 1999; Greko, 2000) and less so in DCs (Mitema *et al*., 2001).

The global coalition against poverty and the concerted efforts to combat AIDS are very important strategies within which AR can be contained. Through massive education, sustained prevention efforts will prevent transmission of infections and liberate resources that can be used to combat AR. Pursuance of the millennium development goals and other global partnerships against important development challenges are very critical to containment of AR not only among the DCs but also among the developed nations. Without a bold, concerted action, not only will millions die in Africa, but the entire world will suffer. To allow sub-Saharan Africa to become socially and economically devastated will have a major impact on the economies of every country of the world and impact on AR. The African Comprehensive HIV/AIDS Partnership (ACHAP) is one answer to the problem.

The public–private partnership has provided a new sense of optimism for fighting many devastating pandemics such as AIDS and has given lots of people hope. ACHAP offers all interested parties a multifaceted paradigm that addresses not only the need for ARV medications, but also the other social and medical facets of the HIV/AIDS problem facing sub-Saharan Africa including indirectly the problems of AR.

9. CONCLUSIONS

The problem of AR in DCs is mainly due to poverty and the factors related to it. The problem of resistance is not quite appreciated by most stakeholders as there are more priorities to address such as provision of basic healthcare or sanitation. These overshadow the problems of AR. Containment of AR in DCs therefore will heavily rely on formation of global partnership with developed countries and organisations to formulate and implement integrated mechanisms to sensitise service providers, the policy-makers, and the users to understand the problem and the consequences of lack of control. Prevention and control will require prudent use of existing agents, discovery of new antimicrobial agents, new vaccines and enhanced public health efforts to reduce transmission. AIDS is a very important player in the development and spread of AR. Without making significant headway with AIDS prevention and mitigation and eradication of poverty, the control of AR will remain a secondary issue in DCs.

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