

ANTIMICROBIAL RESISTANCE: THE NEED FOR ACTION IN THE EAST, CENTRAL AND SOUTHERN AFRICA REGION

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About SPS

The Strengthening Pharmaceutical Systems (SPS) Program strives to build capacity within developing countries to effectively manage all aspects of pharmaceutical systems and services. SPS focuses on improving governance in the pharmaceutical sector, strengthening pharmaceutical management systems and financing mechanisms, containing antimicrobial resistance, and enhancing access to and appropriate use of medicines.

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Acronyms

ACT	Artemisinin-Based Combination Therapy
AMR	Antimicrobial Resistance
ARI	Acute Respiratory Infection
ARV	Antiretroviral
EARSS	European Antimicrobial Resistance Surveillance System
ECSA HC	East, Central, and Southern Africa Health Community
MDR-TB	Multidrug-resistant Tuberculosis
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MSH	Management Sciences for Health
MSSA	Methicillin-sensitive <i>Staphylococcus aureus</i>
PEPFAR	U.S. President's Emergency Plan for AIDS relief
RPF	Regional Pharmaceutical Forum
SP	Sulfadoxine-pyrimethamine
SPS	Strengthening Pharmaceutical Systems (Program) [MSH]
STI	Sexually Transmitted Infection
TMP/SMX	trimethoprim+sulfamethoxazole
USAID	U.S. Agency for International Development
WHO	World Health Organization
XDR-TB	Extensively Drug-resistant Tuberculosis

Introduction

After Penicillin went into widespread use in the 1940s, antimicrobials were heralded as “miracle drugs” and “magic bullets.” Today, we know that antimicrobials are more like a double-edged sword than a magic bullet. Microbes have responded to extensive antimicrobial use by evolving mechanisms to become resistant to these treatments. Antimicrobial Resistance (AMR) is indiscriminant, impacting every region and country in the world.

Antimicrobial availability and use have dramatically reduced morbidity and mortality due to infectious disease. Recent global health initiatives (The Global Fund, The President’s Emergency Plan, etc) have significantly increased availability of AIDS, malaria and TB drugs in resource-limited countries.^{1,2} However, increased access presents the risk of rapid escalation of AMR if the medicines are not managed and used properly.³

Resource-constrained countries bear 95% of the global infectious disease burden and rely on effective antimicrobial medicines to treat these diseases. Many infectious diseases, once easily curable, are becoming increasingly difficult and costly to treat as resistance and multi-drug resistance grows. Some diseases which are difficult to treat even with effective medicines become even more complicated and expensive to cure. Additionally, life-saving medical technologies, such as organ transplants, which are dependent on antimicrobials to prevent surgical site infections, are threatened by AMR.⁴

The burden of AMR is growing across drug classes and around the world. We can no longer continue to rely mainly on the strategy of new antimicrobials coming onto the market as the research and development pipeline in this area has significantly dried in recent decades.

Unfortunately, coordinated containment activities have been lacking, especially at the national and regional level. The East, Central, and Southern Africa Health Community (ECSA HC) must consider these factors and work to contain the emergence and spread of AMR in the region.

Purpose of this paper

Recognizing the need for increased AMR advocacy and containment in the ECSA region, the Regional Pharmaceutical Forum (RPF) held a meeting in April 2008 in Uganda in collaboration with the U.S. Agency for International Development-supported Strengthening Pharmaceutical Systems (SPS) Program of Management Sciences for Health.⁵ The main objective of this regional meeting was to review RPF’s role in AMR containment and integrate AMR advocacy

¹ <http://www.theglobalfund.org/en/>

² <http://www.pepfar.gov/>

³ WHO. 2007. Progress in the rational use of medicines. Agenda item 12.17, WHA60.16, 60th World Health Assembly. Geneva: WHO.

⁴ Laxminarayan, R. and A. Malani. 2007. *Extending the Cure: Policy responses to the growing threat of antibiotic resistance*. Washington, DC: Resources for the Future.

⁵ Joshi M., Kirika R., Bura M., Nelson N., Goredema W. 2008. *Technical Report of the Regional Pharmaceutical Forum and Antimicrobial Resistance Meeting, Kampala, Uganda: April 28–30, 2008*. Developed in collaboration with the Regional Pharmaceutical Forum (RPF) of East, Central, and Southern Africa Health Community (ECSA HC). Submitted to the U.S. Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Sciences for Health.

and containment activities in their 2008-2012 Regional Pharmaceutical Strategy. This paper reviews and expands on much of the AMR information shared at that meeting and what must be done to fight this public health threat. It also expresses the urgency for increased advocacy and containment efforts in the region shared by stakeholders at that meeting.

The Global AMR Situation

AMR is a truly global threat and it only appears to be growing. While resistant infections were traditionally seen in hospital acquired infections due to the environmental pressures of high antimicrobial use and disease transmission rate, community acquired resistance is becoming increasingly common. Multi-drug resistance is another rising threat that compounds and further complicates the problem.

All infectious diseases of major public health importance have become resistant to some extent to current (or former) first line agents. Some notable examples include TB, malaria, acute respiratory infections (ARI), sexually-transmitted infections (STIs), bacillary dysentery, and HIV/AIDS.

HIV/AIDS

Resistance to HIV/AIDS is a huge concern in low-resource countries for whom many second-line treatments are prohibitively expensive. Worldwide surveillance shows that ARV resistance occurs in every region (Table 1). The areas of the world with the highest ARV resistance rates (Europe and North America) are also the areas that have been using ARVs the longest and in the highest quantities. As access to these life-saving drugs increase in resource-constrained settings, so too will the risk for resistance.

Region	Resistance to any ARV
Africa	5.5%
South East Asia	5.7%
Latin America	6.4%
East Asia	7.4%
Europe	10.6%
North America	11.4%

Tuberculosis

Drug resistance is commonly associated with TB. Multi-drug resistant TB (MDR-TB) (defined as resistance to at least two first line agents—isoniazid and rifampicin—has spread around the globe with 490,000 cases emerging every year. In 2006 extensively-drug resistant TB (XDR-TB), a form of TB that is resistant to almost all the anti-TB drugs, exploded into the public health consciousness when an outbreak in Kwa-Zulu Natal, South Africa left 52 of 53 cases dead. XDR-TB has since been identified in 49 countries and in every region of the world.⁷

⁶ From WATCH reports, cited in: Maglione, M, et al. 2007. *Antiretroviral (ARV) Drug Resistance in the Developing World. Evidence Report/Technology Assessment No. 156.* AHRQ Publication No. 07-E014. Rockville, MD: Agency for Healthcare Research and Quality.

⁷ Joshi MP, Zagorskiy A. 2008. Is XDR-TB enough to wake you up to the looming dangers of antimicrobial resistance? Paper presented at the USAID Global Health Mini-University at George Washington University School of Public Health and Health Services, Washington DC. Downloadable from <http://www.maqweb.org/miniu/sessions.php>

Malaria

Malaria treatment has seen effective and affordable first-line agents come and go in recent decades. Chloroquine resistance began in Southeast Asia in the 1970s and over the course of 20 years spread around the world. Sulfadoxine-pyrimethamine (SP), which followed chloroquine as the first line treatment, showed signs of growing resistance after only a few years in mainstream use. Resistance to chloroquine and SP are now both highly prevalent in most malaria endemic areas in Africa.⁸ As a result, artemisinin combination therapy (ACT) is now the recommended first-line treatment in many areas. However, there have been reports of resistance even to ACTs from the Mekong Delta region along the border of Cambodia and Thailand.⁹

Acute Respiratory Infections (ARI) and Diarrheal Diseases

ARI and diarrhea are responsible for almost four million deaths in children under five worldwide every year. Common causes of ARIs, such as *S. pneumoniae* and *H. influenzae* have shown high levels of resistance to multiple drugs. *S. pneumoniae* multi-drug resistance to any three drugs is as high as 79.3% in Hong Kong (Table 2) and *H. influenzae* resistance to penicillin ranges from 6-43% depending on the geographic location.¹¹

AMR in the ECSA Region

The ECSA region does not escape this menace. Although comprehensive national and regional data on AMR is lacking for the ECSA region, there are numerous smaller local or facility-based studies which suggest that AMR is already a major problem in ECSA. This existing data can and should be used for immediate advocacy purposes in the region.

Malaria

Effective malaria treatment is vital to the health of millions living in the ECSA region, much of which is endemic for the disease. The region, like elsewhere in the world, has burned through two cheap and effective agents (chloroquine and SP) in the last few decades. ACTs, the current recommended first-line agent for most countries, must be handled with care to ensure that resistance does not emerge as quickly as it did for SP or as completely as it did for chloroquine (Figure 1).

Table 2. *S. pneumoniae* multi-drug resistance to any three drugs¹⁰

Country	Percent multi-drug resistance to any 3 drugs
Italy	22.4%
Saudi Arabia	23.5%
US	25.8%
Mexico	31.1%
Spain	32.9%
South Africa	33.5%
Singapore	39.9%
France	49.1%
Japan	63.1%
Hong Kong	79.3%

⁸ Boland. P.B. 2001. *Drug Resistance in Malaria*. Geneva, WHO.

⁹ SEARO and WRPO. 2007. Containment of Malaria Multi-drug Resistance on the Cambodia-Thailand Border: Report of an Informal Consultation, Phnom Penh, Cambodia, 29-30 January, 2007. Geneva, WHO.

¹⁰ Adapted from: Jacobs and Others 2003. Quoted in: Laxminarayan and colleagues. Drug resistance (Chapter 55, Pages 1031-1051) In: Disease Control Priorities in Developing Countries, 2006.

¹¹ APUA. 2005. GAARD Report

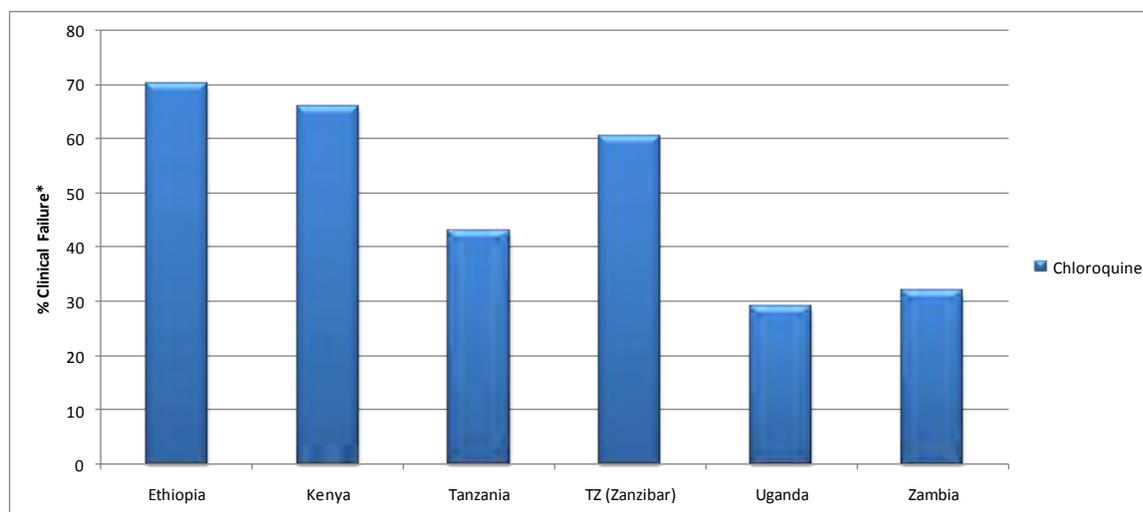


Figure 1. The median percentage of clinical failure rates of chloroquine for several ECSA countries (represents the median of the rates indicated by different studies)¹²

*Represents the median of the rates indicated by different studies

Diarrheal Pathogens

Although most cases of acute diarrhea are self-limiting and do not require antibiotic treatment, the misuse of antibiotics to treat diarrhea has led to the spread of resistance to pathogens that cause severe diarrhea/dysentery and do require antimicrobial treatment. One study found that 85% of *V. cholerae* isolates in Kenya and Somalia were sensitive to chloramphenicol and cotrimoxazole in 1994. Just *two years later less than 10%* were found to be sensitive.¹³

In Kenya, another study of diarrheal pathogens, including *Shigella*, *Campylobacter*, *V. cholerae* and *Salmonella* found that of the cases of diarrhea that were given antibiotic treatment, 51% had pathogens that were not susceptible to the antibiotic given.¹⁴ Although this may reveal the extent of inappropriate prescribing, it also demonstrated the extent of resistance across species to antimicrobials that are commonly relied upon.

Gonorrhoea

Gonorrhoea is another disease that used to be easily treatable with cheap medicines, like penicillin. However, today strains are commonly resistant to not only penicillin but also to several other drugs. In Zimbabwe, a study found that 90% of gonococci isolates were resistant to trimethoprim+sulfamethoxazole (TMP/SMX) and 16% were resistant to tetracycline.¹⁵ The social nature of the disease creates higher selection pressure for resistance in certain groups where transmission and inappropriate treatment are more frequent. The same study found that in the patient sub-population of sex workers 10% of the isolates of gonococci were multi-drug resistant (to penicillin, TMP/SMX, tetracycline and kanamycin).¹⁶

¹² Roll Back Malaria. 2005 World Malaria Report. Website: <http://www.rbm.who.int/wmr2005>

¹³ Materu, SF. et al. *East Afr Med J.* 1997; 74(3): 193-7.

¹⁴ Shapiro, R.L. *J. Inf. Dis.* 2001;183:1701-4

¹⁵ Mason, P.R. et al. *International J of antimicrobial agents.* 1998; 9(3):175-179.

¹⁶ *ibid*

One study in Gondar Health Center in Ethiopia found similarly troubling results— 92.3% of gonococcal isolates were resistant to cotrimoxazole and 87.5% were multi-drug resistant. There was one strain identified that was resistant to eight different drugs, including ceftriaxone.¹⁷

AMR on the Rise

Although resistance rates vary widely by location, organism, and antimicrobial agent, there is mounting evidence indicating that the general global trend is increasing.^{18,19,20} Not only is resistance increasing, but studies have shown that resistance can emerge and increase quickly, in just five to ten years. One study at the National Taiwan University Hospital found that rates of methicillin-resistant *Staphylococcus aureus*, Cefotaxime-resistant *Escherichia coli*, and Cefotaxime-resistant *Klebsiella pneumoniae* between 1981 and 1986 were 4.3%, 0%, and 4% respectively. A decade later, in the period between 1993-1998, the rates were found to have increased sharply to 58.9%, 6.1%, and 25.8% respectively.²¹

Data from the European Antimicrobial Resistance Surveillance System (EARSS) shows that methicillin-resistant *Staphylococcus aureus* (MRSA) rates in the Czech Republic, Slovakia, Hungary and Germany have soared between 2001 and 2005 (from <10% to 13%, 19%, 19%, and 21% respectively: see Figure 2). Eight countries in southern Europe had MRSA levels over 40% in 2005.²²

¹⁷ Tadasse et al. *East African Med J.* 2001; 78(5): 259-61.

¹⁸ WHO. 2007. *World Health Report 2007: A Safe Future; Global Public Health Security in the 21st Century.* Geneva: WHO.

¹⁹ Paladino, J.A., et al. 2002. Review: Economic Consequences of Antimicrobial Resistance. *Surgical Infections.* Vol 3, N3.

²⁰ Jones, R.N. 2001. Resistance Patterns Among Nosocomial Pathogens: Trends Over the Past Few Years. *Chest.* 119;397-404.

²¹ Hsueh et al. *Emerg Infect Dis* 2002; 8(1): 63-8.

²² European Antimicrobial Resistance Surveillance System (EARSS). 2005. *EARSS Annual Report:2005.* Bilthoven, The Netherlands: EARSS.

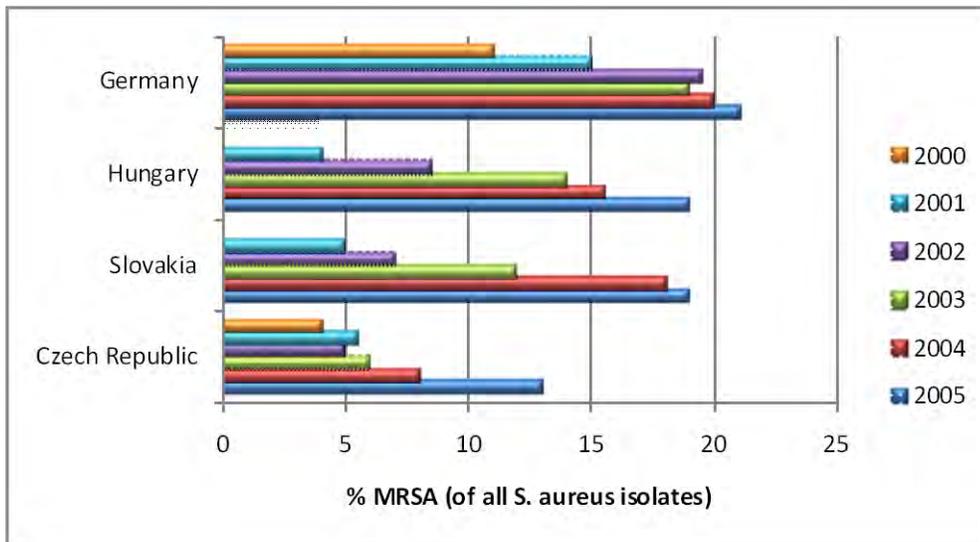


Figure 2. Trends in MRSA Prevalence in Several European Countries between 2000 and 2005

AMR is Rising in the ECSA Region as Well

Just as the ECSA region doesn't escape the AMR burden felt by the rest of the world, it similarly does not escape the alarming trend in increasing AMR rates. For example, in Rwanda *Shigella* resistance to common first line agents (chloramphenicol, ampicillin, and trimethoprim) was found to increase by 40% or more over a 10-year period (Figure 3).²³

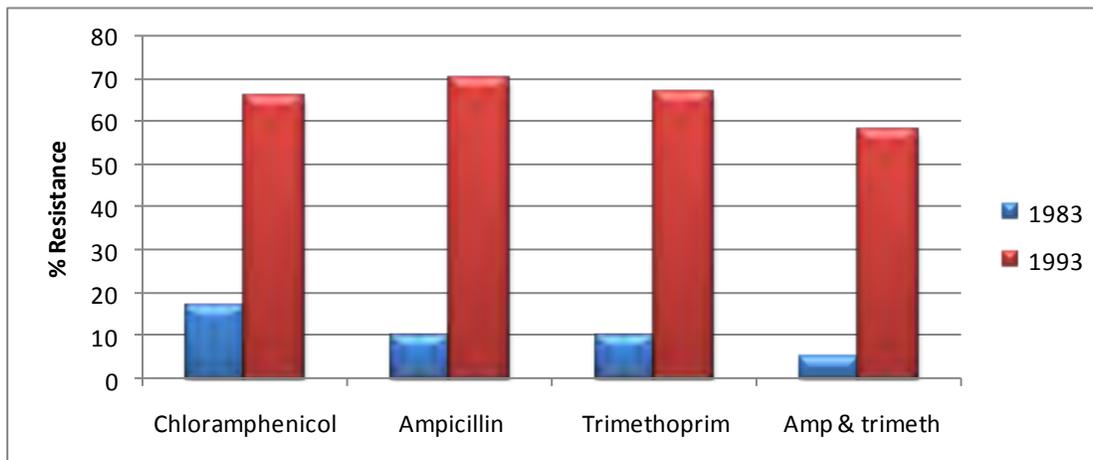


Figure 3. Trends in Resistance of *Shigella* to Several Antibiotics Over a 10 Year Period in Rwanda

²³ Bogaerts, J., et al. 1997. *Diagn. Microbiol. Infect. Dis.* Aug;28(4):165-71

In Kenya, trends in *H. influenzae* resistance to amoxicillin, chloramphenicol and thrimethoprim-sulfamethoxazole was found to increase from 0, 0, and 33% to 65, 34, and 87% respectively between 1994 and 2002 (Figure 4).²⁴

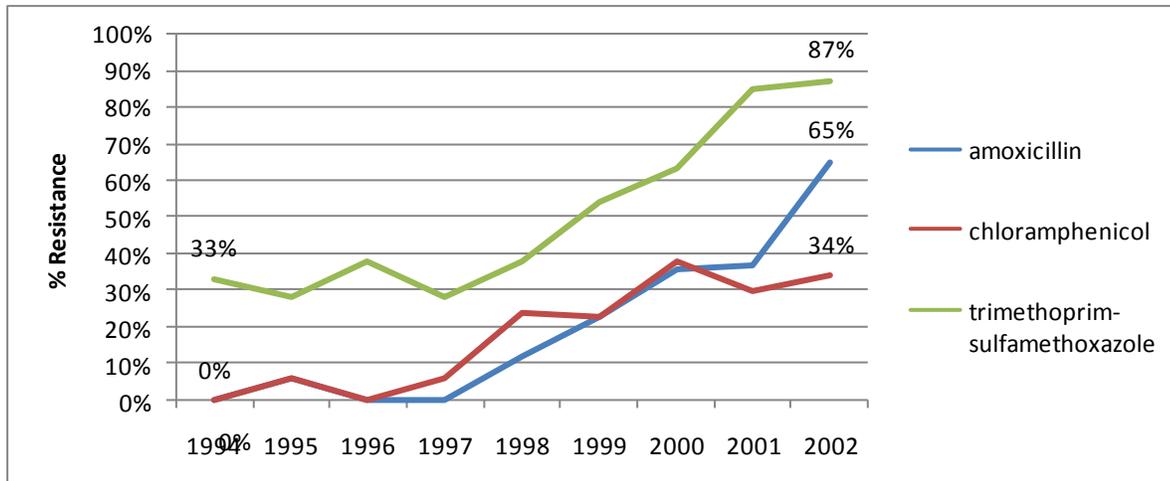


Figure 4. Trends in Resistance of *H. influenzae* to Several Antibiotics at a Hospital in Kilifi, Kenya

These figures are startling and probably represent a limited number of studies that have been published in the literature. Many more cases of resistance undoubtedly go undocumented. The true extent of the problem remains unknown; however we know enough that we must resolve to take action immediately.

The true impact of AMR is equally unknown, although what is known and has been documented is equally startling. If the possibility of losing the effectiveness of reliable antimicrobial medicines doesn't bother us, the individual, societal, and economic costs of AMR should.

The Impact of AMR

The impact of AMR on individuals and society can be staggering. To the individual, a resistant infection means an increased likelihood of treatment failure and prolonged illness and pain, side-effects from second- or third line-drugs, psychological harm from the knowledge of having a "superbug," increased financial burden and greater risk of mortality. Societal costs include burdens on the health system like loss of effective medicines, increased hospital costs (due to increased cost of medicine, more complicated dosing and longer hospital stays), and costs associated with formally switching the first-line treatment for a disease. Costs to the larger society include increased mortality, loss of productivity, and longer period of infectivity, and thus spread, of AMR pathogens.²⁵

²⁴ Scott, J.A.G., et al. 2005. *Antimicrobial Agents and Chemotherapy*. July. Pg. 3021-3024

²⁵ Grandmann, H. et al. 2006. Emergence and resurgence of methicillin-resistant *Staphylococcus aureus* as a public health threat. *Lancet*. 368:874-85.

Another often overlooked consequence of AMR is the loss of life-saving medical technologies that rely on antimicrobial medicines for their effectiveness. Procedures such as chemotherapy, transplants, and other invasive surgery may become too risky to perform if antimicrobials are not available to ward off infections following them.²⁶

The most tangible cost of AMR is the financial impact on individuals and health systems. Although much more research must be done in this area, there are several estimates and anecdotes which suggest that the financial cost of resistance is crippling. The costs associated with AMR in the out-patient settings in the U.S. have been estimated to be between US\$400 million and US\$18.6 billion; the costs among in-patients are likely to be several times more.²⁷

The Canadian Committee on Antibiotic Resistance developed a model that suggested resistant infections add \$14 to \$26 million in direct hospitalization costs to health care cost in Canada—about \$9 to \$14 million more than those infections would have cost had they been drug susceptible. Additional containment measures, such as patient screening and infection control added another \$26 million.²⁸

Second-line treatments, that are often more expensive, are one of the largest parts of the additional cost. Table 3 shows the increased cost of treatment with second-line medicines for three major infectious diseases of global public health importance. In addition to the increased cost of the medicines, there are other costs associated with providing these new drugs that might include the need for more sophisticated monitoring systems, better trained staff, and readiness to act on the increased potential for adverse effects from the use of these powerful medicines.²⁹

²⁶ Laxminarayan, R., et al. 2007. *Extending the Cure*. Washington, DC: Resources for the Future.

²⁷ Okeke et al. 2005. Antimicrobial resistance in developing countries. Part I: recent trends and current status. *Lancet Infect Dis* 2005; 5: 481–93.

²⁸ Canadian Committee on Antibiotic Resistance. 2003. Antimicrobial resistance: A Deadly Burden No Country Can Afford to Ignore. *Canada Communicable Disease Report*. Vol 29-18.

²⁹ Mulligan, JM, C. Morel, S. Meek, A. Mills. “The Costs of Implementing a Change in Drug Policy in Africa: The Case of Combination Therapy for Malaria.” Powerpoint Presentation.
http://mednet3.who.int/icium/icium2004/resources/ppt/O_MA016.ppt

Table 3. Costs of first- and second-line drugs for HIV/AIDS, TB, malaria.

Disease	1 st Line Treatment Cost	2 nd Line Treatment Cost	Increase
HIV/AIDS ³⁰	US\$482/patient/year	US\$6,700/patient/year	+US\$6,218/patient/year (~ 14x more)
Tuberculosis ³¹	US\$20/course	US\$3500/course*	+US\$3480/course (~175x more)
Malaria ³²	US\$ 0.10-0.20/adult course (Chloroquine/SP**)	US\$1.20-3.50/adult course (ACTs***)	+US\$1-2.20/adult course (~6-35x more)

*This is the cost for medicine provided through the green light committee.

** SP—sulfadoxine-pyrimethamine

*** ACT—Artemisinin-based Combination Therapy

Several studies have found that the total cost of treating MRSA compared to methicillin-sensitive *S. aureus* (MSSA) to be up to 3-times more expensive.³³ Table 4 shows the findings of one such study which shows a three-fold increase in hospital stay and total cost of treatment for MRSA compared with MSSA. Another study found that the per diem costs associated with prolonged stay due to MRSA (*not* including laboratory work or medicines) contributed to 77% of the total costs for treating the infection.³⁴

Similarly mortality has also been found to be much higher with MRSA than with MSSA (21% compared to 8%).³⁵ Chloroquine resistance in Africa is considered by some to be the most important single factor behind the doubling of malaria specific mortality in the last 15 years.³⁶

³⁰ Revenga, A. et al. 2006. *The Economics of Effective AIDS Treatment: Evaluating Policy Options for Thailand*. Washington, DC: The World Bank.

³¹ http://www.upmc-cbn.org/report_archive/2006/11_November_2006/cbnreport_111006.html

³² Yeung, S. et al. 2004. Antimalarials Drug Resistance, Artemisinin-based Combination Therapy, and the Contribution of Modeling to Elucidating Policy Choices. *Am. J. Trop. Med. Hyg.* 71(Suppl. 2): 179-86.

³³ Dancer, S.J. 2005. "The Real Cost of MRSA". In *Antibiotic Policies: Theory and Practice*. Ed. Gould and van der Meer. Kluwer Academic/Plenum Publishers, New York.

³⁴ Wakefield, D.S., C.M. Helms, R.M. Massanari, et al. 1988. Cost of nosocomial infection: relative contributions of laboratory, antibiotic, and per diem costs in serious *Staphylococcus aureus* infections. *Am. J. Infect. Control.* 16; 185-192. Quoted in Dancer, S.J. 2005. "The Real Cost of MRSA". In *Antibiotic Policies: Theory and Practice*. Ed. Gould and van der Meer. Kluwer Academic/Plenum Publishers, New York.

³⁵ Dancer, S.J. 2005. "The Real Cost of MRSA". In *Antibiotic Policies: Theory and Practice*. Ed. Gould and van der Meer. Kluwer Academic/Plenum Publishers, New York.

³⁶ Yeung, S. et al. 2004. Antimalarials Drug Resistance, Artemisinin-based Combination Therapy, and the Contribution of Modeling to Elucidating Policy Choices. *Am. J. Trop. Med. Hyg.* 71(Suppl. 2): 179-86.

Table 4. Comparable costs of resistant and susceptible *S. aureus* primary blood stream infections.³⁷

Pathogen	Median hospital stay (days)	Median total cost (US\$)
Methicillin-sensitive <i>Staphylococcus aureus</i>	4	9,661
Methicillin-resistant <i>Staphylococcus aureus</i>	12	27,083

Health care systems around the world are already being significantly impacted by increasing costs associated with AMR. Medicines account for an average of 15% of health expenditure worldwide and 19% of total health expenditure in low-income countries.³⁸ The costs associated with shifting to second line medicines alone can thus put extreme pressures on already stretched health budgets in these low-income countries. For example, second-line ARVs can cost between two and nine times more than first-line ARVs and few generic versions are available. The WHO estimates that without price reductions, second-line ARVs will take up as much as 90% of funds provided for ARV treatment in resource poor countries by 2012.³⁹

AMR must be contained to preserve the effectiveness of these medicines, ensure continued ability to treat life-threatening diseases, and contain health care costs. Although resistance is a natural phenomenon that will occur as long as antimicrobial medicines are used, there are human behaviors that make a considerable contribution to the rapid emergence and spread of AMR. Known interventions implemented by a wide variety of stakeholders can go a long way towards achieving the goal of AMR containment.

Contributing Factors of AMR and Key Interventions

AMR is a complex and multifaceted problem, so it should be expected that the contributing factors to its emergence and spread are diverse and multifaceted as well. Numerous stakeholders from across multiple sectors have a role to play in AMR containment. Once the contributing factors are recognized and prioritized stakeholders can be brought together to begin coordinating and working towards a response to AMR.

Factors Contributing to AMR

The main contributing factors to AMR can be summarized as follows:

³⁷ Abramson MA, Sexton DJ. Nosocomial methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* primary bacteremia. At what costs? *Infect Control Hosp Epidemiol* 1999;20:408-11.

³⁸ WHO. 2004. *World Medicines Situation*. Geneva: WHO.

³⁹ Plus News. *WHO narrows down second-line ARV options*. 7 February 2008.

<http://www.plusnews.org/Report.aspx?ReportId=76633>

- **Inappropriate use of antimicrobial medicines**– inappropriate antimicrobial use is a major driver of resistance. It is estimated that 20-50% of antimicrobial use in humans is unnecessary. Inappropriate use can include behaviors of the prescriber, dispenser and the patient. A breakdown in rational use at any of these places in the drug use cycle can promote resistance. Questionable antimicrobial use in food producing animals such as use for growth promotion is estimated to be 40-80% of all antimicrobial use in animals.⁴⁰ Resistant bacteria can then be transmitted through the food chain to humans or resistant genes developed in animal pathogens can be transferred to human pathogens.
- **Poor Infection Prevention and Control**– poor infection control leads to increased transmission of disease, more illness and thus more need to antimicrobial use leading to increased selection pressure. Additionally, increased transmission aids in the sharing of resistance genes between species. Common modes of transmission include hands and medical devices such as catheters and ventilators.
- **Poor Regulation and Enforcement**– the control of the supply, distribution, and sales of antimicrobials can go a long way in ensuring appropriate use of quality medicines. Antimicrobials sold by street vendors or “over the counter” without a prescription are often used unnecessarily, thus promoting resistance. Many countries have laws in place requiring prescriptions for antimicrobials; however they are often poorly enforced.
- **Poor Quality Antimicrobial Products**– Counterfeit and substandard drugs contribute to resistance by delivering sub-therapeutic levels of the active ingredient in antimicrobial medicines. This means that even if prescriber, dispenser and patient use are all appropriate, they are still undermined by substandard drugs and resistance can develop. The US Food and Drug Administration estimates that 10% of drugs worldwide are fake and in many parts of Africa it is as high as 30%.⁴¹
- **Lacks of Surveillance**– There are two parts to surveillance for AMR: monitoring resistance levels and trends, and monitoring antimicrobial use. Without functional surveillance systems in place, locally effective, focused, and evidence-based strategies cannot be implemented or measured. This also includes pharmacovigilance, which increasingly is being seen as including AMR as a part of therapeutic ineffectiveness.
- **Weak Pharmaceutical Management**– Weak pharmaceutical management system typically manifests itself as inappropriate selection and use (due to lack of policies, guidelines, standard treatment guidelines, essential medicines lists, pre-service and in-service training), undependable supply (stock-outs, etc), and poor storage practices.
- **Drug Advertising and Promotion**– direct to consumer advertising and pharmaceutical promotion targeting prescribers often biases patients and prescribers towards “latest”

⁴⁰ Wise et al. *British Medical Journal* 1998; 317(7159): 609–10.

⁴¹ International Medical Products Anti-counterfeit Taskforce (IMPACT). 2006. Counterfeit Medicines: An update on estimates. Available at <http://www.who.int/medicines/services/counterfeit/impact/TheNewEstimatesCounterfeit.pdf>

drug when existing treatments may still work perfectly well. This influence on the prescribers and patients leads to increased use of new antimicrobials which can lead to their resistance sooner.

Key Interventions to Containing AMR

The interventions that can be implemented to help tackle these weaknesses and contributing factors are known and have been outlined and documented in the WHO's *Global Strategy for Containment of Antimicrobial Resistance*.⁴² This key document provides a framework of interventions to slow the emergence and reduce the spread of antimicrobial resistance and practical guidance to implementation in line with national realities. The framework focuses on the following areas–

- Reduce disease burden and spread of infection
- Improve access
- Improve antimicrobial use
- Strengthen health systems and their surveillance capacity
- Enforce regulation and legislation
- Encourage new drugs and vaccines development

This framework promotes a multifaceted approach which targets a number a stakeholder groups and sectors to include patients/general community, prescribers and dispensers, hospitals, use in food-producing animals, national governments and health systems, vaccines & drug development, pharmaceutical promotion, and international aspects of containing AMR. Details of key intervention areas can be found in the WHO Global Strategy, and regional level interventions relevant to the ECSA context are explored further in the technical report of the 2008 RPF-SPS AMR meeting in Uganda.⁴³

Successful operationalization of the Global Strategy, and thus AMR containment, is guided by country-level coordination of AMR containment activities among stakeholders and strong advocacy at the country and regional levels. National and regional level mobilization and coordination of resources for AMR and rational medicine use can be an effective catalyst to local level action and real change.

Why Must We Act Now?

Although resistance has been known for decades, the global health community has been slow in responding to the threat in force. Consequently the situation has progressively and rapidly gotten worse and continues to do so. It is imperative that there is no further delay in action to contain resistance. There are three reasons why it is more important now than ever to take action– first-line treatments are failing, the new antimicrobial pipeline is dwindling, and the flow of medicines to resource-constrained settings is dramatically increasing.

⁴² WHO. 2001. *Global Strategy for Containment of Antimicrobial Resistance*. Geneva, WHO.

⁴³ Joshi M., Kirika R., Bura M., Nelson N., Goredema W. 2008. *Technical Report of the Regional Pharmaceutical Forum and Antimicrobial Resistance Meeting, Kampala, Uganda: April 28–30, 2008*. Developed in collaboration with the Regional Pharmaceutical Forum (RPF) of East, Central, and Southern Africa Health Community (ECSA HC). Submitted to the U.S. Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Sciences for Health.

First-line Treatment Failure

The beginning of this paper discussed a number of diseases for which resistance was becoming a major problem, both in the ECSA region and around the world. First-line treatments which have been relied upon increasingly need to be replaced by drug which are more expensive and have more side effects on the patient and often more complicated dosing. This has a myriad of impacts also detailed previously. The situation is becoming increasingly dire for many infectious diseases of public health importance (Table 5).

Table 5. Global AMR Rates for Diseases of Major Public Health Importance⁴⁴

Infectious Disease	AMR Global Prevalence Rates
Malaria	Chloroquine resistance in 81/92 countries
Tuberculosis	0-17% primary multi-drug resistance
HIV/AIDS	0-25% primary resistance to at least one antiretroviral agent
Gonorrhea	5-98% penicillin resistance and 1-50% fluoroquinolone resistance in <i>Neisseria gonorrhoeae</i>
Pneumonia and bacterial meningitis	0-70% penicillin resistance, 6-43 % ampicillin resistance, and 11-72% Macrolide resistance in <i>Streptococcus pneumoniae</i>
Diarrhea: shigellosis	10-90% ampicillin resistance 5-95% cotrimoxazole resistance
Hospital infections	070% resistance of <i>Staphylococcus aureus</i> to all penicillins and cephalosporins

A Dwindling Antimicrobial Pipeline

Several decades back resistance to an antibiotic, such as penicillin, wasn't seen as a huge concern since research and development in the pharmaceutical industry was regularly discovering and producing new antimicrobials. In fact, in 1967, the U.S. Surgeon General William H. Stewart declared the war on infectious diseases to be won.⁴⁵ Unfortunately, this proclamation was premature. In the 1990s antimicrobial discovery and production began to stall. Pharmaceutical companies have increasingly focused their efforts in the past decades on drugs for chronic diseases.

The number of new antimicrobials approved by the U.S. FDA has been declining in the last several decades. Figure 5 shows this steady downward trend.⁴⁶

Although there have been recent efforts to work out incentives for companies to develop new antimicrobials through public-private partnerships, progress has been slow and it can take a decade or more to develop and approve a new drug.⁴⁷ With the pipeline of new drugs running

⁴⁴ WHO country data, 2000-03; and APUA. 2005. Global Advisory on Antibiotic Resistance DATA (GAARD Report). Boston: Alliance for the Prudent Use of Antibiotics.

⁴⁵ Medscape General Medicine. 2000.

⁴⁶ Spellberg *et al.* Clinical Infectious Diseases 2008;46:155-64.

⁴⁷ Laxminarayan, R., et al. 2007. Extending the Cure. Washington, DC: Resources for the Future.

dry we can no longer rely only on new technology to save us; we must work diligently to preserve the effectiveness of the medicines we have.

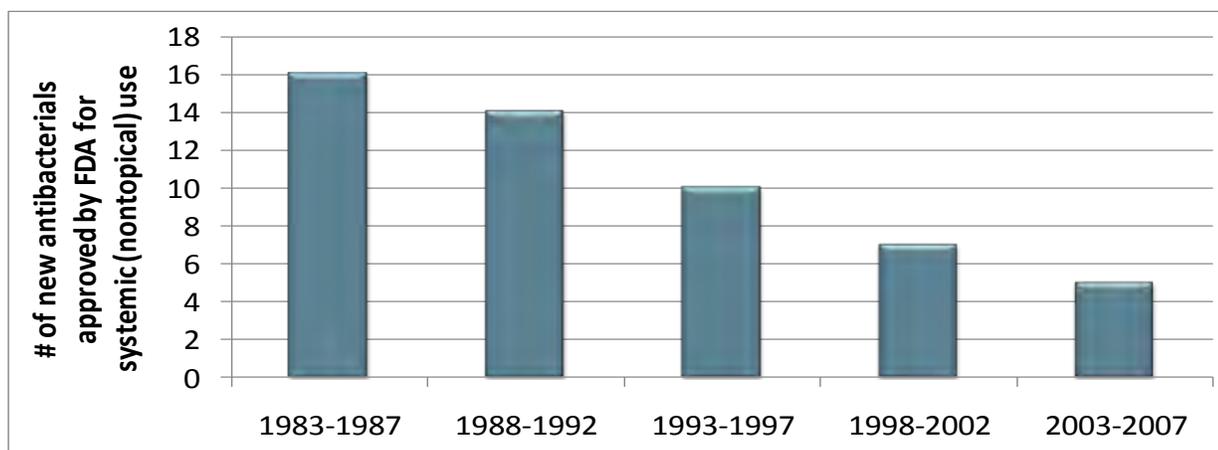


Figure 5. Number of New Antimicrobials Approved by the U.S. FDA between 1983 and 2007

Increased Flow of Medicines to Resource-constrained Settings

Recent global initiatives such as the Global Fund for AIDS, TB, and Malaria; President's Emergency Plan for AIDS Relief (PEPFAR); the Global Drug Facility; and others have gone a long way in improving access to crucial life-saving drugs for millions of people in the ECSA region and Africa in general. However, as the supply of drugs flowing into the region increases, so does the risk of resistance emerging to these drugs if they are irrationally used. Serious consideration must be given to developing the necessary infrastructure and mechanisms to support system strengthening, and the appropriate handling and use of these drugs. If resistance develops, the access will have only been increased to useless medicines and much money and opportunity will have been wasted.

Urbanization and Increased Mobility

Demographics in the ECSA region are changing. The portion of the populations living in town and cities is growing. Several studies have found that urban dwellers are more likely to carry resistant microbes than those that live in rural areas.^{48,49,50} This trend could be explained by increased disease transmission due to denser populations or perhaps greater antimicrobial selection pressure from a higher exposure to antimicrobials due to an increased access to health care.

Another trend in the ECSA region is increasing mobility. Many that move to urban areas travel back and forth between a rural home and the city. Other mobile populations such as workers and displaced people and refugees present opportunity for the spread of resistant infections.

⁴⁸ Nys S, Okeke IN, Kariuki S, Dinant GJ, Driessen C, Stobberingh EE. [Antibiotic resistance of faecal *Escherichia coli* from healthy volunteers from eight developing countries](#). J Antimicrob Chemother. 2004;54:952–5.

⁴⁹ Lamikanra A, Okeke IN. A study of the effect of the urban/rural divide on the incidence of antibiotic resistance in *Escherichia coli*. Biomed Lett. 1997;55:91–7.

⁵⁰ Blomberg, B. 2007. Antimicrobial Resistance in Bacterial Infections in Urban and Rural Tanzania. Thesis for PhD at the University of Bergen. Bergen, Norway.

Additionally, Africa and the ECSA region are increasingly connected to the rest of the global as people move in and out of the countries and the continent, thus potentially importing and exporting resistant pathogens.

AMR does not recognize national borders. Therefore no single country can contain resistance on its own, even within its own territory. All countries must work together under an organized regional strategy and share information and experiences and harmonize policies and procedures if AMR is to be adequately addressed.

Call-To-Action on AMR Containment

AMR is a major threat to health in the ECSA region. If action is not taken now to preserve the effectiveness of antimicrobial medicines, AMR will severely undermine regional and national efforts to manage infectious diseases and meet the Millennium Development Goals by 2015. Access to the essential medicines has significantly increased in the ECSA region, but resistance threatens their continued usefulness. Therefore it is of paramount importance that all stakeholders work together to combat this problem.

No individual country or group can successfully contain AMR alone. Therefore, leadership for AMR containment advocacy at the regional level is crucial to promote strategic coalition and partnerships to advance sustained AMR advocacy and containment at the regional, country, and local levels. The Regional Pharmaceutical Forum (RPF) is an established mechanism within the ECSA Health Community to improve pharmaceutical management in the region. Therefore RPF is well placed within the region to champion AMR and rational medicines use issues. The RPF acknowledges that many AMR containment activities are being implemented, but are often uncoordinated at the local, national and regional levels.

Therefore, through the AMR Call-to-Action document developed during the regional AMR meeting held in Uganda in 2008,⁵¹ the RPF has strongly urged all stakeholders including government, academia, regulatory authorities, professional associations, donor groups, civil society, media personnel, and industry to join hands against the common threat of AMR and start immediate advocacy and containment actions in the ECSA Region.

⁵¹ Joshi M., Kirika R., Bura M., Nelson N., Goredema W. 2008. *Technical Report of the Regional Pharmaceutical Forum and Antimicrobial Resistance Meeting, Kampala, Uganda: April 28–30, 2008*. Developed in collaboration with the Regional Pharmaceutical Forum (RPF) of East, Central, and Southern Africa Health Community (ECSA HC). Submitted to the U.S. Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Sciences for Health.