

Overview of Antimicrobial Resistance

Review of the Cesarean-section Antibiotic
Prophylaxis Program in Jordan and Workshop on
Rational Medicine Use and Infection Control

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Organized by Ministry of Health, Royal Medical Services, and Jordan Food and
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Outline

- Introduction
- Global situation of AMR
- AMR in Jordan
- Impact of AMR
- Global interventions to contain AMR
- MSH/SPS activities to contain AMR
- Summary



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Introduction

- The availability and use of antimicrobials and improvements in other health-related areas during the 20th century resulted in a decrease in morbidity and mortality and an increase in life expectancy.
- However, the recent rapid increase in antimicrobial resistance (AMR) now threatens our ability to treat infections and reverse the achievements of key infectious disease programs in such areas as acute respiratory infections, diarrhea, tuberculosis (TB), and malaria.

For more information, please see:

WHO. 2000. *The Essential Drugs Monitor*. No. 28 & 29. Geneva: WHO. <<http://mednet2.who.int/edmonitor/>>; WHO. 2002.

Antimicrobial Resistance. Fact sheet no. 194. <<http://www.who.int/mediacentre/factsheets/fs194/en/>>; WHO. Drug Resistance.

<<http://www.who.int/drugresistance/en/>>.



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Introduction—Why is AMR a Global Concern?

- AMR Kills – Infections caused by resistant microorganisms often fail to respond to the standard treatment, resulting in prolonged illness and greater risk of death
- AMR increases the cost of health care – when infections become resistant, more expensive therapies must be Used. The longer duration of illness and treatment, often in hospitals, increases health-care costs and the financial burden to families and health systems



Introduction—Drug Resistance Levels in Infectious Diseases

Infectious Disease	Primary Causative Agent	Illustrative Drug and Resistance Levels	Resistant to Other Drugs
Acute Respiratory Infection	<i>S. pneumoniae</i>	Penicillin: Up to 55%	Yes
HIV/AIDS	Human immunodeficiency virus	Antiretrovirals: Up to 25%	Yes
Diarrheal Disease	<i>S. dysenteriae</i>	Co-trimoxazole: Up to 95%	Yes
TB	<i>M. tuberculosis</i>	Isoniazid: Up to 39%	Yes
Malaria	<i>P. falciparum</i>	Chloroquine: Up to 88%	Yes
Skin Infections	<i>S. aureus</i>	Methicillin: Up to 68%	Yes

Sources: Modified from 2003 World Health Report; WHO. 2005 Containing Antimicrobial Resistance; WHO Policy Perspectives on Medicines, and Disease Control Priorities in Developing Countries, “Drug Resistance” Chapter 55. Laxminarayan, R. Extending the Cure , 2007



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Global Situation of AMR (1)

- Pathogens causing TB, malaria, sexually transmitted infections, typhoid, bacterial dysentery, and pneumonia are now resistant or multidrug-resistant (MDR).
- Up to 18% of TB is MDR (and can be higher in some countries). And, extensively drug-resistant (XDR) TB is now being recorded in countries worldwide.
- In 81 of 92 malaria-prevalent countries, chloroquine is no longer effective.

Source: WHO. 2004. *Country Data 2000–03, Containing Antimicrobial Resistance, Policy Perspectives on Medicine*, Nov 20. Geneva: WHO.



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Global Situation of AMR (2)

- ***Salmonella typhi***
 - Multidrug resistance emerged as a public health problem in Asia.
- ***Shigella***
 - Resistance to ampicillin, tetracycline, co-trimoxazole, and chloramphenicol is widespread in Africa.
 - Up to 90% resistance to ampicillin and co-trimoxazole has been found in parts of Asia.
 - Resistance is emerging to fluoroquinolones, the only available option to left for treatment.
- ***Vibrio cholera***
 - Up to 90% of isolates are resistant to at least one antibiotic.

Sources: Okeke, I.N., et al. 2005. Antimicrobial Resistance in Developing Countries. Part I: Recent Trends and Current Status. *Lancet Infectious Diseases* 5(8):481–93. WHO. 2004. *Country Data 2000–03*.



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Global Situation of AMR (3)

- ***Streptococcus pneumonia***
 - Penicillin and erythromycin resistance is an emerging problem in community-acquired pneumonia in Argentina, Asia, Brazil, Kenya, Mexico, and Uganda.
 - MDR (penicillin + two other classes) in Africa is 25%; in the Far East, 63%; in the Middle East, 18%; in Latin America, 20%; in eastern Europe, 12%; in western Europe, 18%; and in the United States, 26%.

Source: Okeke, I.N., et al. 2005. Antimicrobial Resistance in Developing Countries. Part I: Recent Trends and Current Status. *Lancet Infectious Diseases* 5(8):481–93.



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Global Situation of AMR (4): Running Out of Options—Example of *N. Gonorrhoea*

- Widespread resistance to penicillin and tetracycline resulted in replacement with more expensive first-line medicine. Penicillin resistance ranges from 9 to 90% across Asia and is over 35% in sub-Saharan Africa and the Caribbean.
- Replacement medicines also developed resistant problems, azithromycin resistance was found in 16%-72% in the Caribbean and South America, and quinolone resistance is commonly reported in Asia and Africa.
- The only option remaining may be a very expensive third-generation cephalosporin.

Source: Okeke, I.N., et al. 2005. Antimicrobial Resistance in Developing Countries. Part I: Recent Trends and Current Status. *Lancet Infectious Diseases* 5(8):481–93.



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Situation of AMR in Jordan

- About 1/3 of Jordan's health expenditure is for pharmaceuticals and antimicrobials account for a large share of pharmaceutical (23% by Jordanian Dinar and 15% by unit)
- Local stakeholders have expressed concern over the growing antimicrobial resistance in both the community and hospital setting

Source: Rational Antibiotic Use in Jordan: Auditing Antibiotic Use by Targeting Surgical Prophylaxis at Jordanian Hospitals, JFDA, April 2011



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Situation of AMR in Jordan

- Concerns about the inappropriate use of antimicrobials are widespread
 - JFDA study of 2009 showed inappropriate use of antimicrobials in surgical prophylaxis (multiple antibiotics in multiple doses)
 - Medicine use study in Irbid found a very high percentage of antibiotic use in clinics - 60.9%.
 - Other studies (RDU Strategy Development Workshop, 2004) have shown that non-adherence to medications and frequent use of antibiotics for coughs, cold, and flu
- Other studies of AMR in Jordan are described on the following slides



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AMR in Jordan

- Retrospective review was conducted at the ICU at King Hussein Medical Hospital between Jan 2007 and Jan 2008. 610 blood cultures were obtained from 400 patients
- Most common gram negative organism – Acinetobacter
Antimicrobial Susceptibility results:
 - Ciprofloxacin – 45%
 - Amikacin – 39%
 - Imipenen and Piperacillin – 30%
- 48% of the Acinetobacter isolates were multi-drug resistant

AMR in Jordan (2)

- Antimicrobial resistance was studied in 100 *Mycobacterium tuberculosis* strains in Irbid.
 - 19% of isolates were found resistant to at least one of the antituberculosis drugs (rifampin, isoniazid, ethambutol) using allele-specific PCR. 14% resistance was detected using drug susceptibility testing
 - 6 isolates were classified as MDR-TB (resistant to both INH and rifampin)
- These results highlight the importance of molecular epidemiology studies of tuberculosis in understudied regions to uncover the true prevalence of the MDR-TB

AMR in Jordan (3)

Study was conducted to investigate antimicrobial resistance pattern of E.coli strains isolated from clinical specimens, Jan-Dec 2008. A total of 444 strains were isolated and tested for susceptibility.

Results:

Higher Resistance

- Ampicillin - 84 %
- Amox/clav -74.3%
- Cotrimoxazole – 71%
- Naladixic Acid – 47.3%
- Cephalothin – 41%

Lower Resistance

- Cefotaxime/ceftriaxone - 11%
- Ciprofloxacin - 14.5%
- Gentamicin - 17.3%
- Cehalexin -20.9%
- Ceftazidimie – 22.5%
- Cefixime – 29.6%

AMR in Jordan (4)

- The European Antimicrobial Resistance Surveillance System (EARSS) indicates some of the highest levels of bacterial resistance are concentrated in the southeastern Mediterranean region
- Antibiotic resistance in Jordan including *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Escherichia coli* have been well documented through this system from 1996-2011.
- Percentage of non-susceptibility to penicillin and erythromycin in *Streptococcus pneumoniae* isolates: (n=39)
 - Penicillin non-susceptibility – 32%
 - Erythromycin non-susceptibility – 24%
- Resistance in *Staphylococcus aureus* (n-385)
 - Oxacillin (methicillin) non-susceptibility – 64%
- Resistance in *E.coli* isolates (n-214)
 - Fluroquinolone non-susceptibility – 30%
 - 3rd Generation cephalosporin non-susceptibility - 29%

AMR in Jordan (5)

- 166 *Klebsiella pneumonia* strains were isolated from Jan to Dec 2008 and tested for susceptibility to different antimicrobials
- Results
 - High resistance rates
 - Ampicillin – 91.3%
 - Imipenem – 90.9%
 - Piperacillin – 86.3%
 - Ceftriaxone – 83.8%
 - Aztreonam – 83.3%
 - Vancomycin – 80.6%
 - Lower rates of resistance
 - Ciprofloxacin – 6.9%
 - Norfloxacin – 15.1%
 - Naladixic Acid – 33.6%
 - Gentamicin – 39.7%

AMR in Hospitals

- Up to 10% of admitted patients contract hospital-acquired infections. Hospital-acquired infections are among the most prevalent cause of death in the developing world.
- The hospital is a significant source of medicine-resistant infections.
- Important hospital pathogens include—

Methicillin resistant Staphylococcus aureus, Enterococcus faecium, E. faecalis, E. coli, Klebsiella pneumoniae, Enterobacter spp., Citrobacter spp., Pseudomonas aeruginosa, and Acinetobacter calcoaceticus



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Nosocomial Infections and AMR

- Nosocomial infections are contracted by a patient or staff member while in a hospital or health care facility (and not present or incubating on admission)
- Nosocomial transmission of commonly encountered, community-acquired, multidrug resistant organisms includes pneumococcus, *Mycobacterium tuberculosis*, *Salmonella*, *Shigella*.
- Horizontal transfer of resistant genes from one strain to another can also exacerbate the possibility of resistant nosocomial infections.

Source: Okeke I. N., et al. 2005. Antimicrobial Resistance in Developing Countries. Part I: Recent Trends and Current Status. *Lancet Infectious Diseases* 5(8):481–93.



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Impact of AMR

- Individual and public health consequences are enormous in terms of—
 - Increased morbidity and mortality
 - Prolonged periods of infectiousness with increased risk of transmission of the resistant pathogen to others
 - Increased direct cost (longer hospital stay, use of more expensive second- or third-line medicines)
 - Indirect costs (e.g., prolonged absence from work)



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Impact of AMR: Cost Implications (1)

Disease	Avg. First-Line Cost (USD)	Avg. Second-Line Cost (USD)	Increase
HIV/AIDS ¹	482/patient/year	6,700/patient/year	6,218/patient/year (~14x more)
TB ²	20/course	3,500/course	3,480/course (~175x more)
Malaria ³	0.10–0.20/adult course (Chloroquine/sulfadoxine-pyrimethamine)	1.20–3.50/adult course (artemisinin-based combination therapy)	1-2.20/adult course (~6–35x more)

Sources:

1. Revenga, A. et al. 2006. *The Economics of Effective AIDS Treatment: Evaluating Policy Options for Thailand*. Washington, DC: The World Bank.
2. http://www.upmc-cbn.org/report_archive/2006/11_November_2006/cbnreport_111006.html
3. Yeung, S. et al. 2004. *Am J Trop Med Hyg*.71(Suppl. 2): 179-86.



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Impact of AMR: Cost Implications (2)

Antiretrovirals

- Second-line ARVs can cost between 2 and 9 times as much as first-line drugs, and few generic versions are available.
- The World Health Organization (WHO) has estimated that without price reductions, by 2012 as much as 90% of the funds for providing ARV treatment will be spent on second-line drugs.

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

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



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Impact of AMR: Reduced Effectiveness of Medical Technology

- Antimicrobials complement many other medical technologies that require the drugs to ward off infections, such as—
 - Transplants
 - Chemotherapy
 - Surgery
- Ineffectiveness of antimicrobials has indirect costs by limiting the value of these technologies.



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Major Contributing Factors to AMR

- Inappropriate use of antimicrobials
- Use of antimicrobials in animals
- Poor infection control practices
- Inadequate regulation and enforcement
- Poor quality of antimicrobials
- Inadequate AMR surveillance
- Weak pharmaceutical management
- Drug promotion



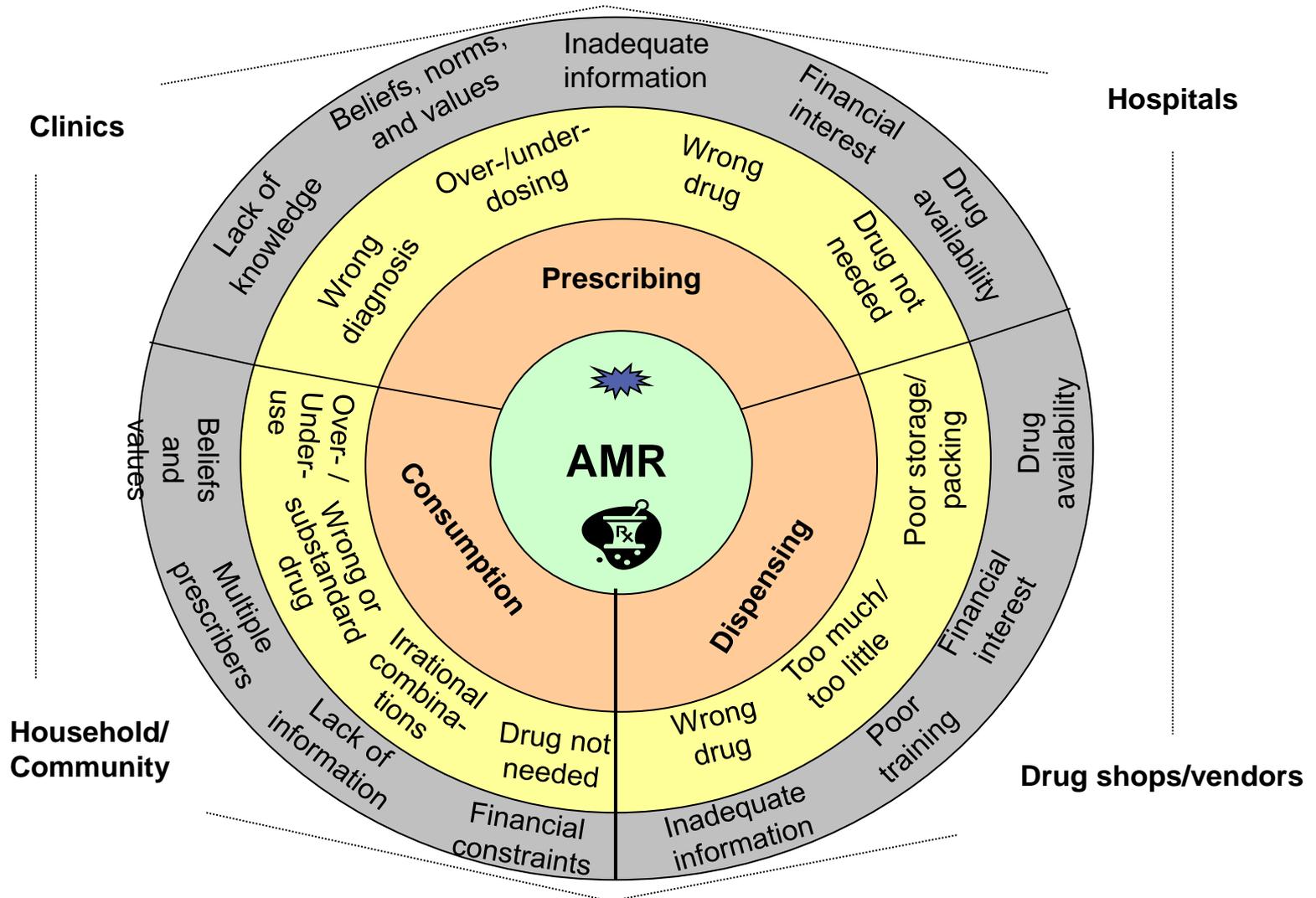
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Real World Factors Impacting Use



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The Global Initiatives and the Risk of AMR Escalation

- Increased flow of antiretrovirals (ARVs), TB, and malaria medicines through international assistance (for example, the Global Fund to Fight AIDS, Tuberculosis and Malaria; U.S. President's Malaria Initiative)
- Resistance likely to escalate if this significant medicine inflow is not matched by strengthened medicine management and AMR prevention activities



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A Complex Problem Requiring Multiple Solutions (1)

- AMR is an overarching issue involving public health, clinical medicine, and microbiology
- This complex multifactorial problem requires multifaceted approach for its prevention and control



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A Complex Problem Requiring Multiple Solutions (2)

- Requires multiple interventions directed toward education, regulation, surveillance, and research
- Requires involvement of all stakeholders—government, academia, NGOs, consumers and communities, health care providers, professional bodies, private sector, cooperating agencies, international bodies



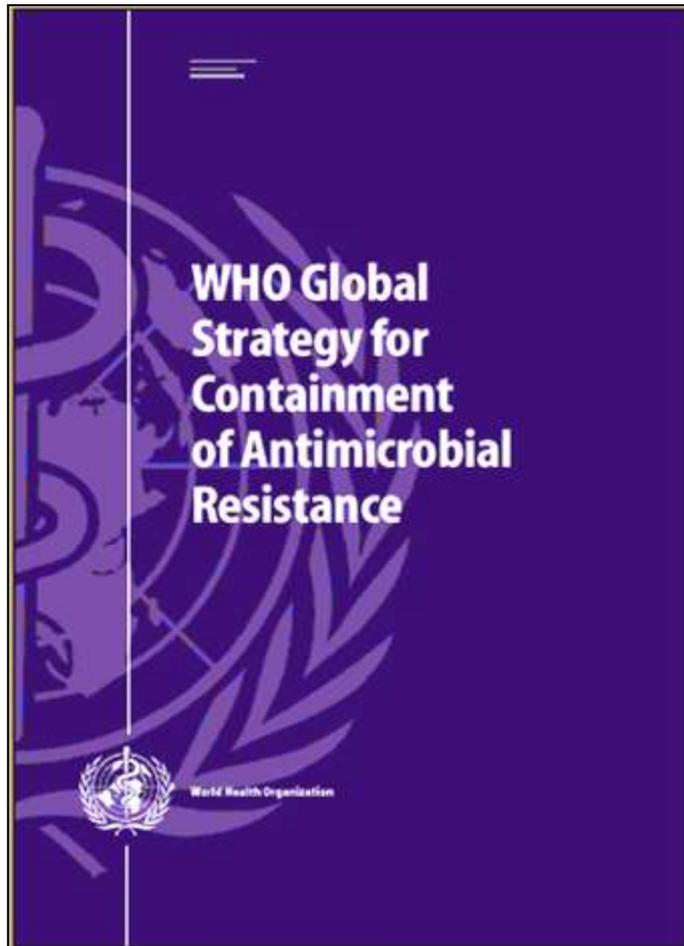
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WHO Global Strategy



- A framework of interventions to slow the emergence and reduce the spread of antimicrobial resistance
- Background information on magnitude and factors responsible for increasing resistance
- Assessment of issues around appropriate antimicrobial use and specific interventions needed to contain resistance
- Practical guide to implementation in line with national realities



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WHO Interventions

- Directed toward—
 - Patients and the general community
 - Prescribers and dispensers
 - Hospitals
 - National governments and health systems
 - Drug and vaccine development
 - Pharmaceutical promotion
 - International aspects of containing AMR



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Key Areas of Intervention

- Reduce the disease burden and the spread of infection
- Improve access to appropriate antimicrobials
- Improve use of antimicrobials
- Enforce legislation and regulations
- Strengthen health systems and their surveillance capabilities
- Encourage the development of appropriate new medicines and vaccines



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Reduce the Disease Burden and Spread of Infection (1)

Community

- Prevent infection through such methods as immunization, vector control, use of bed nets
- Reduce transmission of infection in the household and the community with improved hand washing, personal and household hygiene



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Reduce the Disease Burden and Spread of Infection (2)

Hospital

- Improve hospital infection control practices
 - Hand hygiene
 - Barrier precautions
 - Isolation procedures
 - Disinfection and sterilization
 - Sterile techniques for using invasive devices
 - Perioperative surgical prophylaxis
 - Environmental cleaning and waste management
- Conduct active surveillance of infections, antimicrobial use, and AMR and share results with prescribers



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Containing AMR: Everyone Has a Role

- Different stakeholders, including prescribers, dispensers, hospital managers and administrators, consumers, governments, NGOs, academicians, industry, and others can contribute in various ways to contain AMR
- The hospital infection control team plays the important role of preventing and controlling hospital acquired infections, including resistant infections



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MSH/SPS AMR activities

- Health gains achieved by priority public health programs, including HIV/AIDS, tuberculosis and malaria are increasingly threatened by AMR
- However, few AMR containment programs have been implemented in low-resource countries
- Recognizing this gap, SPS collaborated with country and regional level stakeholders to strengthen their capacity to catalyze AMR advocacy and containment actions



Source: Capacity-Building for Country and Regional Level Advocacy and Interventions to Contain AMR in Africa. SPS. International Conference on Improving Use of Medicines (ICIUM), Nov 2011



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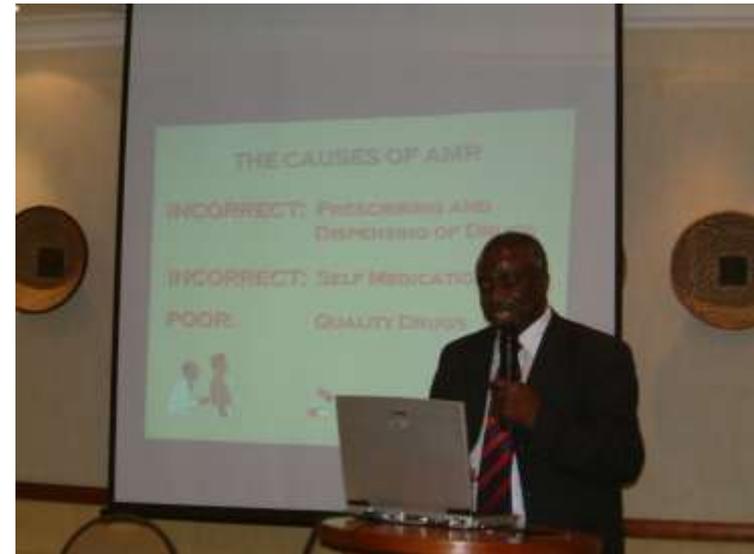


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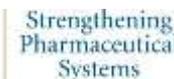


MSH/SPS Activities (2)

- Zambia and Ethiopia initiatives show that national stakeholders are ready to join hands and take actions to support AMR advocacy and containment efforts
- Regional Pharmacy Forum and EPN initiatives demonstrate that existing regional organizations can be mobilized to expand the scope and impact of AMR initiatives
- Such initiatives bring a wide range of stakeholders from various sectors to a single common platform to generate a shared vision, build widespread coalitions, and mount organized actions to contain AMR



Capacity-Building for Country and Regional Level Advocacy and Interventions to Contain AMR in Africa. SPS. ICIUM 2011



MSH/SPS Activities—Policy Implications and Conclusions from Implementation of AMR Activities (3)

- The WHO has provided a Global Strategy on AMR, but few countries are implementing it (ICIUM 2004)
- Effective advocacy and coalition-building is vital for catalyzing an organized, coordinated, and sustained response to the challenge of AMR
- Only when the issue gets sufficient attention and gets identified as an urgent priority can policy decisions at national and local levels take place, including those relating to antibiotic policies, drug regulation, antimicrobial use in animals, AMR surveillance, and education, and research
- Therefore, donors, development partners and key national stakeholders need to provide proactive support for creating sustained advocacy and local coalitions around AMR

Source: Capacity-Building for Country and Regional Level Advocacy and Interventions to Contain AMR in Africa. SPS. ICIUM 2011



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Summary

- First-line therapies are failing for treatment of common infectious diseases
- Development of new antimicrobial is steadily decreasing
- Multifold increase in supply of medicines through recent global health initiatives (Global Fund, U.S. Presidential Initiatives, GDF, etc)
- Resistance likely to escalate rapidly if strategies to strengthen pharmaceutical management and contain AMR are not implemented
- So we must **act NOW** to preserve the effectiveness of currently available antimicrobials



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