Containing Antimicrobial Resistance: Guide for USAID Missions to Promote Institution-Based Interventions

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Containing Antimicrobial Resistance: Guide for USAID Missions to Promote Institution-Based Interventions

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About RPM Plus

RPM Plus works in more than 20 developing and transitional countries to provide technical assistance to strengthen pharmaceutical and health commodity management systems. The program offers technical guidance and assists in strategy development and program implementation both in improving the availability of health commodities—pharmaceuticals, vaccines, supplies, and basic medical equipment—of assured quality for maternal and child health, HIV/AIDS, infectious diseases, and family planning and in promoting the appropriate use of health commodities in the public and private sectors.

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CONTENTS

ACKNOWLEDGMENTS VII

ACRONYMS IX

WHY DO USAID MISSIONS NEED THIS FIELD GUIDE? 1
The Phenomenon of AMR 1
Public Health and Cost Implications 2
Key Factors Contributing to the Emergence and Spread of AMR 3
USAID Commitment to AMR Containment 3
AMR Containment: A Global Challenge 4
How to Use This Field Guide 5

SECTION 1. A NAVIGATION MAP TO INSTITUTION-BASED AMR CONTAINMENT 7
AMR Containment in Institutions 8

SECTION 2. STRENGTHENING ANTIMICROBIAL MANAGEMENT CAPACITY FOR CONTAINING AMR: SELECTED INTERVENTIONS RECOMMENDED FOR USAID MISSIONS 11
1. Developing and Implementing Drug and Therapeutics Committees in Health Facilities 11
2. Development and Maintenance of Hospital Essential Medicines Lists and Formularies 14
3. Development of Standard Treatment Guidelines in Health Care Facilities 16
4. Dissemination and Implementation of Standard Treatment Guidelines 18
5. Investigating Antimicrobial Use and Implementing a Medicines Use Evaluation Program in Hospitals 20
6. Training to Develop and Implement Hospital Infection Control Programs 23
7. Development and Implementation of AMR Containment Training Material for 25
Continuing Medical Education Programs 25
8. Prepackaging Medicines to Improve Case Management of Infectious Diseases 27
9. Improving AMR Surveillance Capacity in Developing Countries 29
Rationale 29

REFERENCES 33

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The U.S. Agency for International Development (USAID) supported the development of the WHO *Global Strategy for the Containment of Antimicrobial Resistance* (AMR) in 2001 and is also supporting its operationalization at the country level through a systematic approach that aims to build and expand local coalition for AMR advocacy and containment. The approach and experiences gained thus far in implementing it are described in the book, *Building Local Coalitions for Containing Drug Resistance: A Guide.* This AMR Field Guide is a complementary document and is primarily designed to assist USAID mission staff to think through some of the key institution-based interventions that the missions can support to help preserve effectiveness of treatments used through priority programs.

The first version of the interventions contained in this guide was developed collaboratively by Management Sciences for Health (MSH) through the Rational Pharmaceutical Management Plus Program (RPM Plus), Harvard Drug Policy Research Group through the Applied Research on Child Health Project (ARCH), Academy for Educational Development (AED) through the CHANGE Project, and the Alliance for the Prudent Use of Antibiotics funded through RPM Plus.

This current version of the guide was coordinated and prepared by the RPM Plus Program. RPM Plus works in more than 20 developing countries to provide technical assistance to strengthen drug and health commodity management systems. The program offers technical guidance and assists in strategy development and program implementation both in improving the availability of health commodities—pharmaceuticals, vaccines, supplies, and basic medical equipment—of assured quality for maternal and child health, HIV/AIDS, infectious diseases, and family planning and in promoting the appropriate use of health commodities in the public and private sectors.

Anthony F. Boni (USAID) identified the need for this guide to support USAID health programs in the field, in addition to providing conceptual guidance and inputs throughout the development process. The main contributors to the contents of this guide were Mohan P. Joshi, John Chalker, Nick Nelson, Terry Green, and Sarah Paige (MSH), Dennis Ross-Degnan (Harvard), Nancy Pollock (AED), and Anibal Sosa (APUA). Special thanks to those who reviewed this document, especially Anthony F. Boni and Veerle Coignez (USAID), David Lee, Maria Miralles, Wonder Goredema, Niranjan Konduri, and Catherine Mundy (MSH), and Susan Foster (APUA).

ACRONYMS

AMR	antimicrobial resistance
CME	continuing medical education
DTC	drug and therapeutics committee
EML	essential medicines list
HIV/AIDS	human immunodeficiency virus/acquired immunodeficiency syndrome
MDR	multidrug-resistant
MoH	Ministry of Health
MSH	Management Sciences for Health
MUE	medicines use evaluation
NGO	nongovernmental organization
QC	quality control
QI	quality improvement
RPM Plus	Rational Pharmaceutical Management Plus (Program) [MSH]
SOP	standard operating procedure
STI	sexually transmitted infection
STG	standard treatment guideline
TB	tuberculosis
TOT	training of trainers
USAID	U.S. Agency for International Development
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

WHY DO USAID MISSIONS NEED THIS FIELD GUIDE?

Over the last six decades, antimicrobials have played an instrumental role in reducing morbidity and mortality from infectious diseases such as HIV/AIDS, tuberculosis (TB), malaria, and acute respiratory infections.[1] However, there is now increasing evidence that antimicrobial resistant pathogens are rapidly emerging and spreading at alarming rates. The global escalation of antimicrobial resistance (AMR) threatens the progress made against infectious diseases over the last 60 years.[1] More importantly, AMR has the potential of creating a significant public health problem of its own, with far reaching implications in terms of cost and health system capacity. The existing strategies to prevent further spread of AMR which are outlined in his field guide will help the U.S. Agency for International Development (USAID) Missions fight this growing threat.

The Phenomenon of AMR

AMR occurs when an antimicrobial medicine recommended to treat an infectious disease pathogen is no longer effective in killing or suppressing that pathogen. Table 1 shows current resistance rates for major public health diseases. Once resistance to first-line medicines develops, second- or third-line agents are required for effective treatment. These second- or third-line agents are often less effective, more toxic, and more costly than first-line agents. When resistance develops to two or more antimicrobials, the result is multidrug resistance (MDR). In early 2006, an extensively drug-resistant TB (XDR-TB) strain (resistant to 3 of the 6 classes of second-line drugs) killed 52 of 53 individuals with identified cases in South Africa.[2, 3] XDR-TB has since been identified in all regions of the world.[*]

Table 1. Global Prevalence Rates of AMR for Infectious Diseases of Major Public Health Importance.

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

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

[*] http://www.who.int/mediacentre/news/notes/2006/np23/en/index.html

Public Health and Cost Implications

Initially, AMR was most prevalent in hospitals, particularly in newborn nurseries, intensive care units, and surgical units. Poor infection control, poor hygiene, and misuse of antimicrobials in hospital wards led to spread of AMR in these settings. Recently, however, AMR has appeared outside of hospitals in communities, as exposure to antimicrobials increases and inappropriate use persists.[4] This silent growth of AMR within communities further threatens public health programs against infectious diseases.

The combination of hospital- and community-acquired AMR is particularly worrisome given that recent global health initiatives such as the Global Fund to Fight AIDS, TB and Malaria; Global Drug Facility [Stop TB/World Health Organization–WHO]; Roll Back Malaria Initiative; the President's Malaria Initiative, and the World Bank's Multi-Country HIV/AIDS Program for Africa have increased the availability of antimicrobial agents exponentially for HIV/AIDS, TB, and malaria in resource-limited countries. Without effective and well-implemented pharmaceutical management plans to match this increased availability and use of medicines, AMR may rise rapidly, rending the few valuable medicines less effective or even ineffective. Counting on the availability of improved or new medicines in the future may not help; there is a scarcity of new antimicrobials in the pipeline, [5] which reduces the likelihood of continued success through empiric antimicrobial treatment in the long term.

The cost implications of AMR, for the individual as well as for society as a whole, are enormous. Table 2 shows the increased cost of switching to second-line medicines for HIV/AIDS, TB, and malaria. These figures reflect only the cost of the medicine, so the real cost, including additional expenses such as prolonged hospital stays or staff training are much higher. Escalation of AMR will not only drain individual but also hospital and ministry of health (MoH) budgets, compromising other essential programs and services.

Table 2. Costs of First- and Second-Line Drugs for HIV/AIDS, TB, Malaria.

Disease	First-Line Cost (USD[**])	Second-Line Cost (USD[*])	Increase
HIV/AIDS[*†]	482/patient/year	6,700/patient/year	6,218/patient/year (~14x more)
TB[‡]	20/course	3,500/course[§]	3,480/course (~175x more)
Malaria[**]	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)

[*] U.S. dollars

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

[‡] http://www.upmc-cbn.org/report_archive/2006/11_November_2006/cbnreport_111006.html

[§] This is the cost for medicine provided through the Green Light Committee (GLC).

[**] 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.

Key Factors Contributing to the Emergence and Spread of AMR

The key factors that contribute to the rapid emergence and spread of AMR are well known. They include first and foremost (1) inappropriate antimicrobial prescribing and dispensing by health providers, and (2) inappropriate self-medication, including poor adherence, by patients. Both practices contribute to "irrational use of medicines."

The practices are the result of several factors, such as cultural conceptions, patient demand for antimicrobials, economic incentives for prescribers and dispensers, direct-to-consumer advertising by pharmaceutical industry, and insufficient training of health professionals. Economic hardship also often leads to terminating treatment early or sharing medicines within the family. Further underlying factors include limited access to health care facilities, poor storage and distribution conditions for medicines, and unregulated availability of medicines, including poor quality and counterfeit products[6]. Additionally, expanding global trade, rapid international travel, and increasing urbanization also facilitate the spread of resistant microbes throughout the world. Finally, irrational and excessive use of antimicrobials in animals also contributes to the AMR problem in humans.

USAID Commitment to AMR Containment

To the same extent the key contributing factors to AMR are known, consensus exists on the strategies to contain the threat. In 2001, WHO developed a *Global Strategy for the Containment of Antimicrobial Resistance* based on evidence and expert consensus. The interventions focus on six key areas (1) reducing the disease burden and spread of infection, (2) improving access to appropriate antimicrobials, (3) improving use of antimicrobials, (4) strengthening health systems and their surveillance capacities, (5) enforcing regulations and legislation, and (6) encouraging the development of appropriate new drugs and vaccines.[7]

USAID provided significant support in developing and launching the 2001 WHO Global Strategy and its background documents. AMR containment had been identified as a key priority area of the USAID Infectious Disease Objective in 1998.[*] The USAID strategic approach for AMR containment has included the following five components[†]—

- Establishing a global strategy and action plan
- Improving understanding of antimicrobial resistance
- Developing methods to detect antimicrobial resistance
- Responding to data on antimicrobial resistance and medication use
- Preventing and slowing the spread of antimicrobial resistance

[*] The USAID overall health strategy has included a separate infectious disease objective since 1998. When launched, the infectious disease program included four areas: TB, malaria, pathogen/disease Surveillance and response, and AMR containment. The emphasis of the program is on "*work[ing] with partners to prevent diseases, while at the same time utilizing and strengthening health systems for prevention, treatment and control programs.*" http://www.usaid.gov/our_work/global_health/id/amr/index.html (accessed February 2008).

[†] U. S. Agency for International Development (USAID). 2004. USAID's Strategy for Combating Antimicrobial Resistance (AMR). http://www.usaid.gov/our_work/global_health/id/amr/index.html (accessed February 2008).

The interventions recommended in this guide address primarily the last component of the strategy and their implementation at the country level.

AMR Containment: A Global Challenge

Implementation of the WHO Global Strategy at the country-level has been lacking in most resource-constrained countries.[8] Therefore, USAID set out to develop tools and processes for AMR advocacy and containment at the country level specifically adapted to such contexts. The key steps of the approach, developed with the assistance of Rational Pharmaceutical Management (RPM) Plus and partners, involves—

- Gathering information to identify key issues and players
- Forming a country-level multidisciplinary AMR working group to catalyze a response by stakeholders to build and coordinate realistic strategies to contain AMR
- Initiating advocacy efforts and raising awareness of AMR

A document developed to guide this process, *Building Local Coalitions for Containing Drug Resistance: A Guide,*[*] describes the details involved in these steps. The approach has been implemented in Zambia and Ethiopia.[9–14] These steps help guide a systematic approach to AMR containment that can provide a comprehensive and sustainable response. However, the interventions in this field guide can also be individually implemented as value added to existing USAID programs as opportunities arise and conditions allow. USAID Missions are encouraged to assess the in-country context and decide whether a systematic approach is feasible or selected individual interventions are more realistic in the prevailing circumstances.

AMR issues are cross-cutting in nature, so interventions aimed at containing resistance provide an across-the-board benefit of managing and improving medicines use. The interventions included in the following section of this guide offer such wider benefits for improving "systems" and "pharmaceutical management," which are critical for strengthening the overall capacity to contain resistance. At the same time they also provide program-specific benefits by contributing to containing resistance and preserving medicine effectiveness in priority diseases for USAID Missions.

[*] Management Sciences for Health (MSH). 2008. *Building Local Coalitions for Containing Drug Resistance: A Guide*. Arlington, VA: MSH. http://www1.msh.org/projects/rpmplus/loader.cfm?url=/commonspot/security/getfile.cfm&pageid=24155_2.pdf

How to Use This Field Guide

The field guide is divided in two sections. Section 1 is a navigation map providing a general overview of interventions and how they relate to one another to form a multi-faceted AMR containment strategy at the health-institution level. The section includes information regarding the rationale behind the different steps and/or interventions and is intended to help USAID officers think through the different aspects of a (institution-based) AMR containment strategy, and how these components could be integrated into a USAID program activity in the field. Depending on the country, it may be recommended to adopt and implement a comprehensive strategy as a whole, or to limit the activity to one or more distinct interventions.

Once the decision has been made, Section 2 guides USAID officers through the specific activities and issues involved in each of the interventions listed. Section 2 is organized in a menu-like format, providing not only detailed description of the activities involved but also time estimates, factors for cost considerations, and an illustrative lists of monitoring and evaluation (M&E) indicators.

In conclusion, the feasibility, degree of relevance, and priority of the proposed activities will depend on the in-country needs, resources available, government and in-country partners' priorities, and existing in-country expertise. This guide will enable USAID Mission staff to decide on *appropriate* and *feasible* interventions, taking cost and time factors into account.

SECTION 1. A NAVIGATION MAP TO INSTITUTION-BASED AMR CONTAINMENT

Preventing and slowing the spread of AMR is one of the five key areas of the overall USAID strategic approach to AMR containment. To do so, this approach proposes the following key steps at the country level—

- Conduct an initial rapid assessment to identify the main issues and players
- Form a local multidisciplinary AMR group (champion group) to catalyze subsequent actions
- Expand AMR advocacy and coalition
- Implement locally feasible interventions

If the USAID Mission determines that this systematic approach towards AMR containment would be feasible, then a good starting point will be to consult the USAID-supported document *Building Local Coalitions for Containing Drug Resistance: A Guide*[*] The document provides a detailed description of the steps and relevant tools that can be used with some adaptations to suit local contexts. If, however, prevailing conditions do not allow for such a comprehensive approach, effective support for rational medicines use and AMR containment can still be achieved by implementing selected individual interventions described in this field guide.

Developing institution-based AMR containment strategies is important because—

- Hospital-acquired infections have a substantial impact on morbidity and mortality
- Hospitals consume a disproportionate share of healthcare budgets of developing countries
- Hospitals are the major nidus for the emergence of resistant bacteria
- Hospitals amplify resistance, since the bacteria can spread quickly among patients
- Patients who acquire resistant infections in hospitals have the potential to disseminate resistant bacteria into their homes and communities

Although this document focuses on institution-based interventions, note that interventions targeting antimicrobial use and resistance surveillance in the community, quality assurance and other aspects of drug regulation, drug innovation, and veterinary antimicrobial use are also critically important aspects of AMR containment.

[*]Management Sciences for Health (MSH). 2008. *Building Local Coalitions for Containing Drug Resistance: A Guide*. Arlington, VA: MSH. http://www1.msh.org/projects/rpmplus/loader.cfm?url=/commonspot/security/getfile.cfm&pageid=24155_2.pdf

AMR Containment in Institutions

The field guide focuses on nine interventions that contribute to AMR containment within health facilities—

1. Developing and implementing drug and therapeutics committees (DTCs) in health facilities
2. Developing and maintaining hospital essential medicines lists (EMLs) and formularies
3. Developing standard treatment guidelines (STGs) in healthcare facilities
4. Disseminating and implementing STGs
5. Investigating antimicrobial use and implementing a medicine use evaluation (MUE) program in hospitals
6. Training to develop and implement hospital infection control programs
7. Developing and implementing AMR containment training material to integrate into continuing medical education (CME) programs
8. Prepackaging medicines to improve infectious diseases case management
9. Improving AMR surveillance capacity in developing countries

DTCs are multidisciplinary advisory bodies that bring together health care providers and managers to promote safe, effective, and economic use of medicines. The natural environment of a DTC is the hospital, though they can also operate at a national level (guiding hospital DTCs) and in primary health care facilities. DTCs are a key factor in any strategy to contain AMR at the institutional level. Well-functioning DTCs develop, maintain, and ensure implementation of hospital EMLs, formularies, and STGs—three strategic tools to eliminate inappropriate, unsafe, ineffective, and expensive medicines.

EMLs cover medicines deemed essential to satisfy health needs of the vast majority of patients attending a health facility of country. These lists are based on evidence including efficacy, safety, quality, and comparative cost-effectiveness considerations. Formularies are medicine lists with pharmacological data and information. STGs describe the preferred medication and non-pharmaceutical treatments for common health problems; they guide providers in the selection of the most appropriate medicines. All three tools can be applied effectively to discourage the inappropriate use of antimicrobials, which can constitute up to 40 percent of a hospital medicines budget and are often misused.

When considering a health care facility based AMR containment strategy, it is important to determine whether or not DTCs are functioning effectively (or even present) and whether EMLs and STGs not only exist but are also utilized appropriately. Descriptions of possible intervention activities are included in Section II, **interventions 1, 2, 3, and 4**.

An additional intervention where the DTC can play a central role is in introducing and implementing an MUE program. Initial indicator-based antimicrobial use studies to identify problem areas followed by focused MUE programs can effectively remedy specific medicines use problems. The necessary steps for such an intervention are described in detail in Section II, **intervention 5**.

Where DTCs exist, **interventions 2–5** can be effectively implemented as a part of the overall functioning of this body. However, it is important to note that these interventions do not need to be seen as being totally dependent on the existence of a DTC. Depending on the available conditions and opportunities, they can be implemented independently and effectively by motivated staff even in settings that lack DTCs.

Other institution-based interventions that may not have a direct role for DTCs are development and implementation of a hospital infection control program; continuing medical education programs for prescribers; prepackaging of antimicrobials; and improving AMR surveillance capacity (Section II**, interventions 6–9**). Each intervention can have a significant impact, both in terms of health care facility functioning and budget and in terms of AMR containment. Well implemented infection control programs represent a fundamental intervention to prevent hospital-acquired infections, many of which are caused by multidrug resistant pathogens. Periodical exposure to interactive in-service trainings (continuing education) on AMR and appropriate antimicrobial use helps prescribers maintain current and correct knowledge and skills in these areas. Prepackaging of antimicrobials encourages appropriate prescribing by prescribers and adherence by patients. Generating and using local surveillance data contribute to AMR containment by supporting evidence-based decision making.

Each of these interventions has a common goal of containing AMR and should be linked at every opportunity with other relevant actions that are planned or ongoing at the local level. For example, DTCs, STGs, formularies, MUEs, infection control activities, and surveillance can be discussed as value-added topics during AMR-related in-service trainings. Similarly, DTC and AMR surveillance teams can maintain close information exchange to complement each others' actions.

It is important to note that indicator-based monitoring on a periodical basis can serve as a valuable mechanism to measure longitudinal progress and assess any need for program modifications. Some illustrative indicators are provided for each intervention included in this guide to assist in thinking about measurement. Additional indicators may be relevant depending on local program designs.

SECTION 2. STRENGTHENING ANTIMICROBIAL MANAGEMENT CAPACITY FOR CONTAINING AMR: SELECTED INTERVENTIONS RECOMMENDED FOR USAID MISSIONS

1. Developing and Implementing Drug and Therapeutics Committees in Health Facilities

Rationale

A drug and therapeutics committee (DTC) is a multi-disciplinary advisory body in a health care facility that brings together health care providers and managers to promote safe, effective, and economic use of medicines. As such, DTCs are an ideal forum for improving antimicrobial selection and use and for AMR containment.

Specific Activities

Training courses (and follow-up technical assistance where needed) can help build or increase capacity of health care professionals to create, improve, and maintain DTCs in hospitals.

The curriculum, sequence, and length of the training courses can vary according to local context, but the following considerations may be useful for USAID officers regarding the intervention—

- The purpose of the training course curriculum is to (1) promote the establishment of DTCs, (2) train potential and actual members of DTCs, and (3) promote the effective functioning of DTCs on EML, formulary, and STG management issues, identification of medication use problems, and implementation of strategies to improve medicine use.

- The main audience of the course will be physicians, pharmacists, nurses, and health officials in hospitals and primary care clinics. Therefore, the course should address "the nuts and bolts" of a functioning DTC.

- Also, it may be effective to prepare shorter parallel presentations (without the nuts and bolts) to build a constituency in favor of DTC development and implementation among health officials in ministries of health, universities, or private organizations.

The courses can be provided by international facilitators, but that may not be sustainable in the long run and a training of trainers (TOT) may be in order. The TOT approach has the advantage of building in-country and regional capacities to not only establish more DTCs but also to organize local DTC training programs and provide follow-up technical assistance. The training course should be designed so that local academic and health care institutions can take the training materials and institute their own training course using local expertise. During the training course, a plan of action will be developed for broad DTC implementation and for local courses and follow-up.

Arguably, as important as the training courses are, the follow-up activities are equally important and should be part of a "quality assurance mechanism/plan." This plan should include (1)

monitoring medicine use in a health care facility, (2) evaluating use, (3) re-training health professionals in the functioning of DTCs and/or in appropriate use of medicines, where necessary, and (4) implementing new activities that will promote continued improvement in medicine use and formulary management. The quality assurance plan or workplan can be followed up by an internal or external assessment of progress, which in turn can provide the basis for recommendations for further improved DTC implementation.

Note: Frameworks and references for these types of courses exist. Management Sciences for Health (MSH)/RPM Plus (in collaboration with WHO) has developed a training course (including a TOT component) and follow-up framework for international and national courses. The trainer's guide, participants' guides, and visual aids are available from MSH upon request.

Cost Considerations

The cost is highly dependent upon the local motivation and commitment from the Ministry of Health. Costs include the expense of the training facility, course materials (re)production, a secretariat to handle local coordination, local transportation, accommodations, meals, and field site fees.

Time Estimates

To develop and present a DTC course, time recommendations include 2 to 4 months to prepare the course; 12 days for the actual course (with 2 days leeway at the beginning and at the end of the course); 12 months of active follow-up including producing reports on trips, proceedings, etc.; and immediate technical assistance to participants. Members of the local lead group can provide primary follow-up and technical assistance, and can help plan and carry out further courses by the participants with or without outside assistance.

Products

- DTC training course completed

Outcomes

- DTCs instituted in participants' health care facilities, with workplans in place, and activities underway to fulfill the workplan agenda

- Improved prescribing and management of antimicrobials as measured by the hospital and prescribing indicators in a longitudinal manner

Indicators

- Number of DTC training courses completed
- Number of participants in attendance
- Number of health facilities represented at training courses
- Percentage of hospitals (in target area) with a functioning DTC

- Percentage of DTCs that have terms of reference
- Percentage of DTCs that meet more than three times per year
- Percentage of DTCs that have established criteria concerning medicine selection

Hospital indicators[*]

- Availability of a key set of antimicrobials
- Expenditure on antimicrobial drugs as percentage of total hospital drug costs
- Percentage of health care facilities that have an accessible formulary

Prescribing indicators

- Average number of antimicrobial drugs received by patient prescribed antibiotics per hospitalization
- Percentage of antimicrobial drugs prescribed that are consistent with the hospital formulary list
- Average number of doses of antimicrobial drug prophylaxis prescribed for surgical inpatients who received prophylaxis
- Percentage of patients with pneumonia who are prescribed antimicrobial drugs in accordance with standard treatment guidelines (STGs)
- Average duration of prescribed antimicrobial drug treatment
- Percentage of antimicrobials that are injections

[*] Process indicators from the RPM Plus manual "How to Investigate Antimicrobial Drug Use in Hospitals." These indicators are drug use indicators and are not specific to DTCs or to impact of the training course.

2. Development and Maintenance of Hospital Essential Medicines Lists and Formularies

Rationale

Essential medicines lists (EMLs) and formularies are companion documents, with the formulary being an expanded medicines list with pharmacological data and information. Establishing and maintaining national and local EMLs and formularies lead to cost effective medicines procurement and improved availability and use. With regard to antimicrobials, adherence to EMLs and formularies can have a significant impact on antimicrobial selection, use, and effectiveness by eliminating unsafe and ineffective medicines and by enabling consistent and predictable treatment from all levels of providers and at all locations within a health care system. Depending on need, the DTCs of individual facilities can adapt the national EML and formulary to a local context.

Specific Activities

Most developing countries have a national EML and formulary. The EML and formulary lists are compiled epidemiologically, according to medicines needed to treat conditions commonly seen at health care facilities and according to evidence-based criteria such as efficacy, safety, quality, and cost. The process involves a variety of stakeholders including pharmacists, respected clinicians from all levels of the health care system, administration, and nursing staff. Obtaining a broad-base of participation in developing the EML and formulary will more likely result in their adherence and acceptance once they are launched.

After the initial essential medicines list has been developed, it should be kept up to date through a transparent unbiased process with additions and deletions reflecting developments in treatment and revisions in STGs. This process should take place both at national and local levels. The best committee to take on this responsibility within the hospital setting is the DTC, if it exists in the particular health care facility. However, other selection committees may exist within health care facilities that manage the selection process, e.g., the formulary committee.

This activity can be implemented in two different ways—

- Provide technical assistance to local counterparts to develop an EML and an accompanying formulary for the hospital

- Provide technical assistance to developing an effective strategy and process for specific hospitals to implement their own EML and formulary

Cost Considerations

The EML and formulary development costs include training key staff on the principles of formulary management, printing the formulary, and the cost of a consultant. The formulary also needs to be managed over the long term by an institutional committee such as a DTC; these costs should be a part of the hospital management budget. Additional costs for consultants, travel/per diem, training, publication, reproduction, and distribution of the formulary list will be required.

Time Estimates

The time frame depends on the scope of the drug list. If it is a simple list of essential medicines or is based on the WHO's Model List of Essential Medicines, the process of initial drafting, review, and revision may be completed within two to three months. But if the essential medicines list is more complicated and aims at including additional drug information, then the process can take 9-12 months.

Products

- Completed EML or formulary list and/or formulary manual and principles and procedures for managing the formulary

Outcomes

- Improved prescribing and availability of medications including antimicrobials

Indicators

- Percentage of health care facilities that have an accessible EML or formulary
- Percentage of health care facilities with developed principles and procedures for managing additions and deletions to the formulary list
- Number of chemical entities in the EML or formulary
- Number of antimicrobials on the EML or formulary
- Average price of a key set of antimicrobials procured over the past year
- Availability of a key set of antimicrobials
- Percentage of antimicrobials prescribed that are listed on the EML or formulary

3. Development of Standard Treatment Guidelines in Health Care Facilities

Rationale

Experience has shown that even when the medicine supply is based on an approved formulary or essential medicines list, ample opportunity exists for ineffective, unsafe, or wasteful prescribing. Standard treatment guidelines (STGs) can provide expert/consensus guidance to practitioners on appropriate use of antimicrobials and thus discourage the misuse of antimicrobials. *Utilization, however, will not occur on its own by simply providing health care professionals with STGs*—the guidelines must be disseminated and implemented effectively. So, dissemination and implementation are highlighted as an independent intervention in this field guide (see intervention four).

Specific Activities

A weeklong workshop guiding the development and launch of STGs in general, and for the target infectious diseases in particular, can be an effective method to implement this intervention. The key participants might include leading professors from local medical schools and experienced district medical officers and outstanding community health staff. Department heads of major hospitals should also be consulted in preparing the guidelines. It is necessary to involve many staff-level physicians and pharmacists to obtain a broad-based participatory approach, one that will ensure buy-in later when the manual is completed.

Treatment guidelines must have current and accurate information. Therefore, the importance of using both evidence-based medicine that reflects drug efficacy, safety, quality, and cost in preparing the guidelines; and expert authors and a wide range of reviewers cannot be overemphasized. The guideline needs to be revised periodically (every two years, where possible) for continued value.

Effective and strategic implementation and dissemination of STGs is just as important as the development of the guideline and is described in the next section (intervention four).

Cost Considerations

Costs of a week-long workshop (mentioned above) on developing and launching STGs in health facilities include facilitators, venue, participant support and publication and follow-up costs. Since production of STGs is pointless without proper dissemination and implementation, these additional costs should be taken into consideration from the beginning of the process (see intervention four).

Time Estimates

In general, it will take four months to plan and stage the workshop and one year to develop and print the guidelines.

Products

- STG workshop held
- Completed and approved STG

Outcomes

- Improved prescribing of antimicrobials that contributes to better patient care

Indicators

- Percentage of hospitals that have approved STGs
- Percentage of treatments that are prescribed in accordance with STGs
- Percentage of antimicrobials that are prescribed that comply with STGs

4. Dissemination and Implementation of Standard Treatment Guidelines

Rationale

Intervention 3 describes the development of standard treatment guidelines (STGs). However, utilization does not occur automatically. The first step to ensuring that STGs are used effectively in clinical practice is dissemination—making them available—but it doesn't stop there. Active implementation through trainings and other methods to ensure that STGs are used must follow. Without this critical second step, STG development is futile—the use of antimicrobials in hospitals and primary care clinics will not improve and antimicrobial resistance will continue to grow.

Specific Activities

STG implementation will be completed in two phases. It is recommended that a national or regional professional society of physicians who treat the target diseases be identified during phase I. This society can help organize a STG dissemination committee. The committee's role is to implement an interactive half-day, case-based CME program which includes—

- Reviewing clinicians' treatments of patients (anonymously) compared to current STGs
- Identifying discrepancies between the clinicians' prescribing and the approved STGs
- Conducting interactive CME program with presentations of clinicians' aggregated prescribing data and case-based discussions of STG-based treatment approaches
- Distributing STGs and newly developed patient education materials on STGs to participants

During phase II, the dissemination committee conducts a follow-up CME program three to six months after the first program. This CME will again evaluate clinicians' prescribing habits and STGs use. Results of discussions about the challenges will be presented and summarized. The final step will be to send follow-up mailings that will include educational materials, summary of prescribing practices before and after the STG meetings, and a summary of solutions as needed.

Cost Considerations

Costs of developing the program will depend on local circumstances and if outside consultants are involved. The program committee will require a budget for meetings and materials development. International consultants may be needed for some of the proposed programs. To estimate costs, consider planning and preparation time, reimbursement for one international and local consultant, the cost of where to hold the course, materials/supplies and printed educational materials, and a secretariat.

Time Estimates

Phase I which includes developing program materials is estimated to take approximately six months. Preparing for phase II will run about three months.

Products

- CME course organized and completed

Outcome

- STGs are disseminated to clinicians and utilized to improve the use of medicines

Indicators

- Number of clinicians trained at STG dissemination CME conferences
- Percentage of providers who have utilized STGs as a result of CME activities
- Percentage of hospitals that have STGs
- Percentage of treatments that are prescribed in accordance with STGs

5. Investigating Antimicrobial Use and Implementing a Medicines Use Evaluation Program in Hospitals

Rationale

From a clinical standpoint, poor antimicrobial medicine management and inappropriate use by providers, dispensers, and the general public lead to poor health outcomes as well as emergence and spread of antimicrobial resistance. It is recommended that hospitals and other health care facilities investigate their use of antimicrobials and apply ongoing medicines use evaluation (MUE) programs. Such an approach not only provides information on antimicrobial drug prescribing practices within the facility but it also allows for performance comparisons with other hospitals and prescribers and identification of problem areas. Finally, it allows hospitals to orient supervision and assess changes in prescribing practices, if any, resulting from interventions

Specific Activities

A team of investigators representing health care facility administrators, the DTC, local researchers and program managers will lead research on antimicrobial use in hospital settings. A useful tool for the research activity is the manual "How to Investigate Antimicrobial Use in Hospitals: Selected Indicators,"[15] developed by the RPM Plus Program of MSH. Another useful tool is the WHO *How to Investigate Drug Use in Health Facilities: Selected Drug Use Indicators*[*]. The initial antimicrobial use investigation will help identify problem areas. From those findings, hospitals can then develop a program of MUE and initiate locally appropriate activities. MUEs define acceptable criteria and standards of practice, audit actual practices based on these pre-established criteria and standards, identify the problems in practice, analyze causes of the problems, formulate intervention(s) to remedy the problems, implement the intervention, and re-evaluate the practice to measure and monitor improvement.

Cost Considerations

The primary expense associated with participatory assessments of this type will vary depending upon how extensive the research is and how the follow-up MUE is designed. A two-week assessment conducted by three people typically takes 1.5 person months of effort. This encompasses one week of data collection and one week to process information and write a report for each hospital. According to the region and level of technical expertise employed, the estimated cost varies widely.[15]

Collecting data using the manual, *How to Investigate Antimicrobial Use in Hospitals: Selected Indicators*[15], and developing an MUE program can be done locally by hospital and community experts. The cost of conducting an antimicrobial use study and MUEs should be considered a part of the hospitals general operating budget.

[*] World Health Organization, Action Programme On Essential Drugs, WHO/DAP/93.1, Geneva, Switzerland, 1993.

Time Estimates

Time frame depends on the nature of the MUE program. Initial antimicrobial use investigation and analysis of findings followed by undertaking of the specific MUE will take approximately three months.

Products

- Drug use indicator study report
- MUE program plan
- MUE report

Outcomes

- Improved antimicrobial use and treatment practices due to implementation of MUEs targeted towards specific problem areas identified by initial antimicrobial use research.

Indicators

- Number of health facilities completing a drug use indicator study for outpatients
- Number of health facilities completing a antimicrobial drug use indicator study for inpatients
- Number of medication use evaluations completed
- Percentage of prescriptions in compliance with criteria for MUE

Hospital Indicators

- Existence of STGs and a list of officially sanctioned antimicrobial drugs in a formulary
- Availability of key indicator antimicrobial drugs in stock on the day(s) of the study
- Average number of days that a set of key indicator antimicrobial drugs is out of stock in a 12-month period
- Expenditure on antimicrobial drugs as percentage of total hospital drug costs

Prescribing Indicators

- Percentage of prescriptions in compliance with criteria for STGs
- Percentage of hospitalizations with one or more antimicrobial drugs prescribed
- Average number of antimicrobial drugs prescribed per hospitalization with antimicrobial drugs prescribed

- Percentage of antimicrobial drugs prescribed consistent with the hospital formulary list*
- Average cost of antimicrobial drugs prescribed per hospitalization with antimicrobial drugs prescribed
- Average duration of prescribed antimicrobial drug treatment
- Percentage of surgical inpatients who received antimicrobial drug prophylaxis
- Average number of doses of antimicrobial drug prophylaxis prescribed for surgical inpatients who received prophylaxis
- Percentage of patients with pneumonia who are prescribed antimicrobial drugs in accordance with STGs
- Percentage of antimicrobial drugs prescribed by generic name

Patient Care Indicators

- Percentage of doses of prescribed antimicrobial drugs actually administered
- Average duration of hospital stay of patients who receive antimicrobial drugs

Supplemental Indicator

- Number of antimicrobial drug sensitivity tests reported per hospital admission including antimicrobial treatment

* This may or may not be a part of the national essential drugs list or formulary list.

6. Training to Develop and Implement Hospital Infection Control Programs

Rationale

Hospital infection control measures help reduce hospital-acquired infection, thereby decreasing the volume of medicines use and slowing the development of resistance. Preserving the effectiveness of cheaper first-line antimicrobials will ultimately result in less use of more expensive second-line antimicrobial treatments.

Specific Activities

Hospital infection control requires a trained multi-disciplinary team, developing and implementing programs to control nosocomial infections. It may be recommended to pilot the intervention in one or more hospitals, and based on the lessons learned, disseminate the activity to other hospitals

Specific elements of this activity include—

- *Identify and engage teams from participating hospitals (months one-two)*
  Participating hospitals should have support from institutional leadership and commitment to active participation. Teams should be multidisciplinary, including physician, nurse, and at least one other partner such as hospital administrator, quality improvement person, or pharmacist. The team must be given authority to initiate changes in their institution and be willing to serve as opinion leaders and trainers in their institution and beyond.

- *Workshop one: Learning quality improvement (QI) approaches to hospital infection control (month three)*
  This is a three to five day workshop, conducted by a local and international team of facilitators, involving two to three-person teams from each of the four to five participating hospitals. The workshop incorporates field work to practice use of self-administered assessment tools in a local hospital engaged for this purpose. At the end of the workshop, each team develops a plan to implement a QI process in one priority setting.

- *Teams carry out assessments and implement systems changes (months three to seven)*
  After returning to their hospitals, the teams implement plans developed during the workshop with support from local and international facilitators as needed. A four-month period is typically required to implement one QI cycle.

- *Workshop two: sharing experiences and disseminating success (month eight)*
  After completing the first QI cycle, teams reconvene for a two to three day workshop to share experiences from early implementation. This workshop reinforces principles from the first workshop, develops skills in problem solving, and establishes an action plan for disseminating approaches within participating hospitals and to other institutions.

- *Dissemination of infection control activities (months nine to 12)*
  In a process supported by local facilitators, the teams disseminate infection control programs in their own institutions, and help to train teams from other institutions to undertake similar activities. Integrated into these activities is the collection of targeted process and outcome data to evaluate success.

Cost Considerations

The cost of the training depends on local circumstances including the availability of local consultants and motivated teams to oversee infection control programs. Cost considerations for one training cycle including planning and preparation time, reimbursement for one international consultant and one local consultant, the cost of where to hold the course, materials/supplies, and follow-up to participants when they return to their facilities.

Time Estimates

Estimates of time involved for each section of the project are listed above. The entire intervention is estimated to take one year including all workshops and follow-up activities.

Products

- Infection control workshops presented

Outcome

- Hospitals implement infection control policies and procedures to decrease and control nosocomial infections

Indicators

- Percentage of hospitals with infection control policies and procedures
- Number of participants trained, hospital wards assessed ,and QI plans implemented
- Rates of infection prevention or control activities (e.g., hand washing, antiseptic use)
- Rates of nosocomial infections, including those caused by drug-resistant bacteria

7. Development and Implementation of AMR Containment Training Material for Continuing Medical Education Programs

Rationale

To use antimicrobials appropriately, health care professionals require up-to-date knowledge on which antimicrobials are recommended to treat specific infections and which factors contribute to AMR. Professionals also require skills to overcome barriers to the appropriate use of antimicrobials. Interactive in-service trainings or continuing medical education (CME) programs can contribute to knowledge and skill building in appropriate antimicrobial use.

Research in developed countries has shown that interactive CME sessions can effect change in professional practice and, on occasion, health outcomes.[16] In the long term and in conjunction with other interventions, interactive CME sessions combined with provision of patient and professional education materials should improve appropriate use of antimicrobials. Assuming that antimicrobials are largely overused, the intervention would also translate into cost reductions and reduced AMR rates.

Specific Activities

In principle, CME programs for health professionals should already be available in the country, organized by MoH or professional organizations and associations. In this context, the intervention can be focused on developing an AMR component to be integrated into already existing CME programs. To design and implement the CME program, the following specific activities are needed—

- Identify opinion leaders to serve as national AMR CME program committee members, with representatives from professional societies and academia. In its role as sponsor of the national CME program, this committee would—
    - Develop a model AMR CME program or AMR materials consisting of large-group sessions, small group interactive problem solving case discussions, and role-play on overcoming barriers to appropriate antimicrobial use, that can be added to existing CME programs
    - Identify the most important local infections in terms of prevalence or severity of AMR problems to highlight in CME sessions and materials
    - Develop (or modify existing) educational materials (e.g., flowcharts, pocket-sized standard treatment guidelines, etc.) targeting these infections for clinicians to share with peers in practice settings
    - Develop (or modify existing) patient education materials to promote appropriate antimicrobial use for these infections (e.g., posters)
    - Develop (or modify existing) tools to evaluate the CME program and to assess participants' gains in knowledge and skills

- Identify national professional society meetings that professionals who prescribe antimicrobials attend and—
    - Seek agreement of the professional society to integrate a CME program on AMR into the meeting program
    - Identify, invite, and confirm presenters and facilitators for the AMR CME program
- Implement and evaluate the AMR CME program at the national professional society meeting(s).
- Follow-up with mailed reminders and educational materials to participants in the AMR CME program to reinforce learning.

Cost Considerations

The costs of developing the AMR CME program will depend on local circumstances, the availability of local resource materials, and the involvement of outside consultants. The national CME program committee will require a budget for meetings and materials development. The implementation budget is modular and depends on the number of CME sessions held. Each iteration may require funds for facility and media equipment rental; costs of breakfast, tea break, and lunch for participants; costs of printed educational materials and one post-conference mailing; and travel expenses and honoraria for facilitators. Once the infrastructure for the CME is in place, subsequent CME sessions will not be as expensive.

Time Estimates

Once a program committee has been formed, preparation of the AMR CME program and materials is estimated to take about six months. Implementation of the CME Program at professional society meetings can be ongoing.

Products

- Completed CME session

Outcome

- Participants are trained in antimicrobial use and AMR

Indicators

- Number of participants at CME session
- Number of participants by specialty group
- Percentage of participants who improve on CME test scores related to AMR material
- Percentage of participants who evaluate AMR CME programs favorably

8. Prepackaging Medicines to Improve Case Management of Infectious Diseases

Rationale

Prepackaging medicines for treating infectious diseases increases appropriate prescribing by health workers and enhances the ability of patients to understand and adhere to treatment regimens. Studies have also shown that prepackaging certain medicines can reduce costs and decrease the quantities used of these medicines. [17–19]

For example, in 2004 Kenya initiated use of patient kits in their National Leprosy and Tuberculosis Program. Each pack represented complete treatment for one patient, was color coded according to treatment regimen, and included fixed-dose combination medicines. This prepackaging scheme benefited the program by increasing ease of ordering and dispensing medication, facilitating identification of defaulters, and increasing product quality.[19]

Specific Activities

Prepackaging full courses of therapy for the treatment of infectious diseases such as malaria, pneumonia, and sexually transmitted infections (STIs) can be done in the public or private sector, in one facility or in a system. Examples of packaging methods include cutting and sealing polythene bags or using blister packs.

Treatment instructions, pictorial aids, and health education messages can be attached to polythene bags or imprinted on blister packs. Condoms and partner-notification cards can be attached to STI treatment packs.

Specific activities include—

- Select treatment regimens based on locally appropriate standardized treatment protocols
- Prepackage full treatment courses. Packets may be divided into compartments that will each contain a daily dose. Packages for patients of different weights or ages can be color coded or otherwise distinguished.

Develop systems to ensure that an adequate supply of prepackaged drugs is maintained, including sufficient quantities for age and weight categories of patients.

Cost Considerations

Prepackaging equipment and materials must be purchased but the cost of prepackaging materials is only a few cents per pack. If over-prescribing is reduced, costs will actually be reduced. Local consultants may be available to implement this program which will reduce costs substantially.

Estimated start up costs for this intervention include local consultants, development of policies and procedures, packaging equipment (small scale hospital level), developing and pretesting packaging, training staff, and monitoring/quality control.

Time Estimates

Equipment purchase and installation, package design and provider training can be completed in three to six months. The intervention can be evaluated approximately 8-12 months after dispensing of packets begins, depending on patient volume.

Products

- Completed prepackaging system with good guidelines in place

Outcome

- Medications are prepackaged and dispensed resulting in appropriate medicine use and decreased cost

Indicators

- Average waiting time for medication dispensing
- Percentage of patients prescribed the correct drug for the correct number of days
- Percentage of treatments that follow STGs
- Number of stock-outs of prepackaged drugs

9. Improving AMR Surveillance Capacity in Developing Countries

Rationale

AMR surveillance data is an essential component needed for effective management of infectious diseases. The scarcity of diagnostic microbiology laboratories in resource-poor settings, compounded by the lack of trained personnel with the capability to undertake microbiological culture and antibiotic sensitivity testing, has led to the use of empiric strategies for administering antibiotics, resulting in overtreatment and inappropriate use.

Surveillance data can be used to guide infectious diseases treatment and to institute appropriate policies that help prevent AMR. Resistance surveillance data can be employed by STG committees to update guideline recommendations, by individual practitioners to conduct more targeted treatment of individual infections, and by DTCs and infection control committees to take locally appropriate preventive or corrective actions.

AMR surveillance systems vary widely from those with a narrow base, focusing on a few organisms in one disease area, to those covering numerous diseases, organisms, and antimicrobials. Whatever their design, they should be able to detect significant differences and shifts in susceptibility to various antimicrobial agents, and the information derived from them should reach all relevant parties quickly. Surveillance systems achieve better results where epidemiological and microbiological efforts are effectively integrated. Reliable surveillance systems provide the basis for—

- Improving diagnostic practices
- Defining and quantifying AMR in a country
- Guiding the development of standard treatment guidelines
- Establishing thresholds for public health action on AMR issues
- Reducing the inappropriate use of antibiotics
- Containing the emergence or spread of resistant microorganisms

Specific Activities

The first step is to undertake an assessment of any surveillance systems or mechanisms already in place. This situation analysis should include—

- Identification of key stakeholders (MoH, government officials, public autonomous institutions, professional associations, academia, pharmaceutical industry, NGOs, consumers)

- Analysis of the systemic capacity of the organizations involved in surveillance, including the infrastructure for laboratory diagnostic testing

- Assessment of performance and baseline quality level of diagnostic laboratories

- Collection of AMR data and surveillance baseline information by area, if available
- Assessment of the quality of available surveillance data

This assessment endeavors to do several things—have a general overview of systemic surveillance capacity, identify geographic and scientific knowledge gaps, highlight areas of duplicated effort and areas that lack attention, highlight the variability in test methods, and encourage greater harmonization of microbiological and epidemiological basis for surveillance.

The assessment can then form the basis for the second step, developing the implementation strategy. This will involve all levels of the health care system including government, epidemiologists, microbiologists, infectious disease physicians, reference and local microbiology laboratory staff, and clinical staff.

The implementation strategy will depend on the results of the assessment, but overall, the following key elements should be present and functional towards the end of the program[20]—

- AMR surveillance protocol*
- Internationally-recognized standardized methods adapted to local circumstances
- Standard Operating Procedures (SOPs) for laboratory testing
- Internal and external quality control practices
- Screening procedures for major errors and unusual findings
- Procedure for laboratory network reviews

Cost Considerations

Cost will vary widely and include those relating to international and local consultants, situation analysis, protocol development**,** and basic equipment.

Time Estimates

Initial situation analysis and planning would take three to six months. To develop a suitable surveillance system may take much longer, depending on the in-country context.

Products

- Development of AMR surveillance protocol
- Use of an internationally-recognized standardized method for surveillance purposes
- Description of internal quality control (QC) practices and results of QC data collected during the same time period as the data set
- Development of policies and procedures for participation by network laboratories in external quality assurance schemes

* WHONET is a database software developed by WHO for the management of microbiology laboratory data and the analysis of antimicrobial susceptibility test results. It is available on the web at http://www.who.int/drugresistance/whonetsoftware/en/

- Development of policy and procedures for network laboratories and/or the network coordinator to review the results for quality and what corrective actions need to be taken if problems are identified
- Development of screening procedures for major errors and unusual findings
- Description of antibiotic susceptibility testing data for biological and epidemiological plausibility and unusual or unknown phenotypes
- Description of internal consistency through analysis of cross-resistance to related compounds and concordance with other studies

Outcomes

- Availability of levels and trends of AMR for key pathogens and framework for assessing national surveillance capacity
- Improved capacity to develop, implement, coordinate, and evaluate AMR containment strategies
- Improved capacity to apply AMR data to STGs

Indicators

- Written protocols available and in use for antimicrobial sensitivity testing including quality control
- Number of staff participating in surveillance data collection and analysis activities compared with the number of staff required
- Monthly production of standardized AMR data
- Monthly dissemination of data to clinicians and policy makers, DTC, infection control committee
- Monthly reports of internal quality control results
- Percentage of external quality control tests completed correctly

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