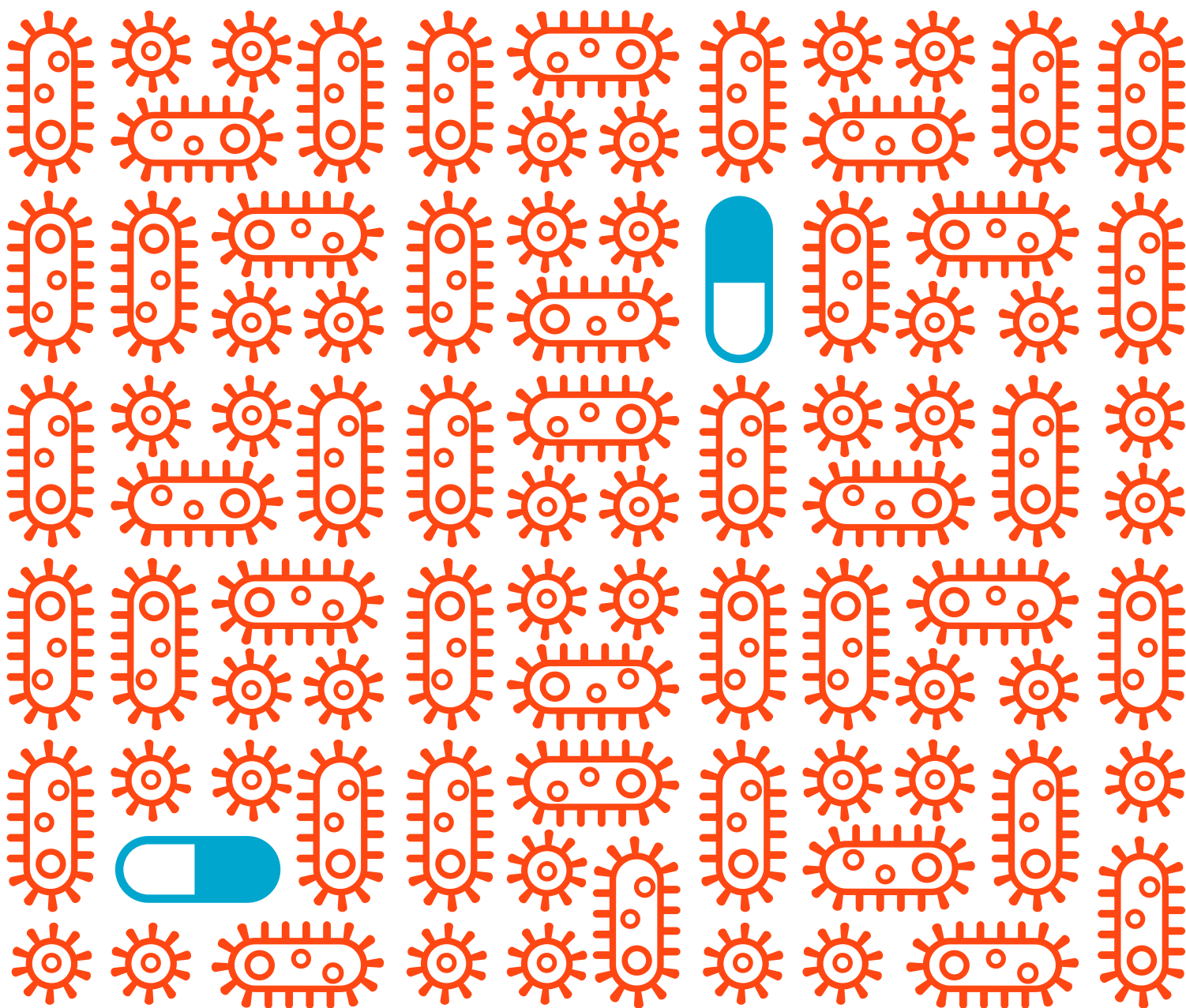


Recommendations for Implementing Antimicrobial Stewardship Programs in Latin America and the Caribbean:

Manual for Public Health Decision-Makers



Pan American
Health
Organization



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Organization
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Americas

FIU

Robert Stempel College
of Public Health
& Social Work

Recommendations for Implementing Antimicrobial Stewardship Programs in Latin America and the Caribbean: Manual for Public Health Decision-Makers

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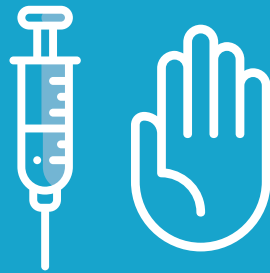
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PREFACE

As a public good, antimicrobial medicines require rational use if their effectiveness is to be preserved. However, up to 50% of antibiotic use is inappropriate, adding considerable costs to patient care, and increasing morbidity and mortality. In addition, there is compelling evidence that antimicrobial resistance is driven by the volume of antimicrobial agents used. High rates of antimicrobial resistance to common treatments are currently reported all over the world, both in health care settings and in the community. For over two decades, the Region of the Americas has been a pioneer in confronting antimicrobial resistance from a public health perspective. However, those efforts need to be stepped up if we are to have an impact on antimicrobial resistance and want to quantify said impact.

In response to antimicrobial resistance, countries in the Americas developed and began the implementation of national action plans aligned with the Global Action Plan on Antimicrobial Resistance of the World Health Organization (WHO). The purpose of national plans is to provide guidelines to reduce the impact of antimicrobial resistance and, insofar as possible, to ensure continued treatment and prevention of infectious diseases with drugs that are safe, effective and of good quality, are used responsibly, and are accessible to those who need them. One key strategic line of action in those plans is optimizing the use of antimicrobial medicines in human and animal health. The plans also address the need for countries to establishing stewardship programs “that monitor and promote optimization of antimicrobial use at national and local levels in accordance with international standards in order to ensure the correct choice of antimicrobials at the right dose, based on evidence.” The current recommendations are meant as guidance to public health decision makers who need to plan and implement antimicrobial stewardship programs, both in hospitals and primary care centers.

The Pan American Health Organization (PAHO) and the Global Health Consortium at the Florida International University (GHC-FIU) share a strong commitment to public health, and joined forces to try to contain the upward trends of antimicrobial resistance and their health, welfare and economic consequences. In this context, these recommendations are a joint effort to assist public health decision makers at national and local levels, as well as hospital managers, in their contribution to the fight against antimicrobial resistance. As the reader will notice, public health relevance is emphasized throughout.

Written and edited by experts in the field, this manual examines the concept and benefits of antimicrobial stewardship programs, and describes their major components: leadership, human resources, microbiology laboratories, and robust pharmaceutical services. Specific interventions are described, as are the ethical and legal issues related to these programs. Primary health care interventions are given special attention, as over 90% of antimicrobial use occurs at the community level, where high antibiotic use may reflect over-prescription, easy access through over-the-counter sales, and, more recently, internet sales, which are widespread in many countries.

Authors and contributors to these guidelines are recognized experts in antimicrobial stewardship from Latin America and the Caribbean, who have direct experience in the implementation of these programs. We would like to express our appreciation to all who provided their expertise, enthusiasm, and hard work to develop this publication. Its scope and structure were defined during an expert consultation carried out by the GHC-FIU in collaboration with PAHO in April 2017.

Finally, we would like to stress that antimicrobial stewardship programs work to prevent harm, improve patient safety, and succeed in reversing increasing rates of antibiotic resistance. These programs improve and measure the appropriate use of antibiotics to optimize clinical outcomes, minimize unintended consequences, such as toxicity, and reduce the selection pressure on bacterial populations that leads to the emergence of resistance.

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Acronyms and abbreviations

AMR	ANTIMICROBIAL RESISTANCE
AMS	ANTIMICROBIAL STEWARDSHIP
ASP	ANTIMICROBIAL STEWARDSHIP PROGRAM
ATC	ANATOMICAL THERAPEUTIC CLASSIFICATION
ATCC	AMERICAN TYPE CULTURE COLLECTION
CDC	CENTERS FOR DISEASE CONTROL AND PREVENTION
CDI	<i>CLOSTRIDIUM DIFFICILE</i> INFECTION
CDSS	CLINICAL DECISION SUPPORT SYSTEMS
CLSI	CLINICAL LABORATORY STANDARDS INSTITUTE
CML	CLINICAL MICROBIOLOGY LABORATORY
CNS	CENTRAL NERVOUS SYSTEM
DDD	DAILY DEFINED DOSES
DOT	DAYS ON THERAPY
ESBL	EXTENDED SPECTRUM BETA-LACTAMASE
FIU	FLORIDA INTERNATIONAL UNIVERSITY
HCW	HEALTH CARE WORKER
ICU	INTENSIVE CARE UNIT
IDSA	INFECTIOUS DISEASES SOCIETY OF AMERICA
INRUD	INTERNATIONAL NETWORK FOR RATIONAL USE OF DRUGS
IPC	INFECTION PREVENTION AND CONTROL
MDR	MULTIDRUG RESISTANCE
MIC	MINIMUM INHIBITORY CONCENTRATION
MOH	MINISTRY OF HEALTH
MRSA	METHICILLIN RESISTANT <i>STAPHYLOCOCCUS AUREUS</i>
OECD	ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT
PAHO	PAN AMERICAN HEALTH ORGANIZATION
PHC	PRIMARY HEALTH CARE
PIDS	PEDIATRIC INFECTIOUS DISEASES SOCIETY
SHEA	SOCIETY FOR HEALTHCARE EPIDEMIOLOGY OF AMERICA
VRE	VANCOMYCIN-RESISTANT ENTEROCOCCI
WHO	WORLD HEALTH ORGANIZATION
WTO	WORLD TRADE ORGANIZATION



Part I

General aspects

I.1. Introduction

Gabriel Levy Hara, Hospital Carlos
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Antimicrobials have saved millions of lives worldwide. However, antimicrobial resistance (AMR) threatens said achievements and poses serious risks to human health. It is also a rapidly evolving problem worldwide (1). Progressive loss of antibiotic options challenges not only high-complexity acute care hospitals as it daily affects the community, as well. Some examples of prevalent pathogens with growing resistance in community and hospital settings (2) are listed below, and figure 1 shows a recently released World Health Organization (WHO) priority pathogens list to guide research and development of new drugs (3).

COMMON PATHOGENS WITH INCREASING RESISTANCE

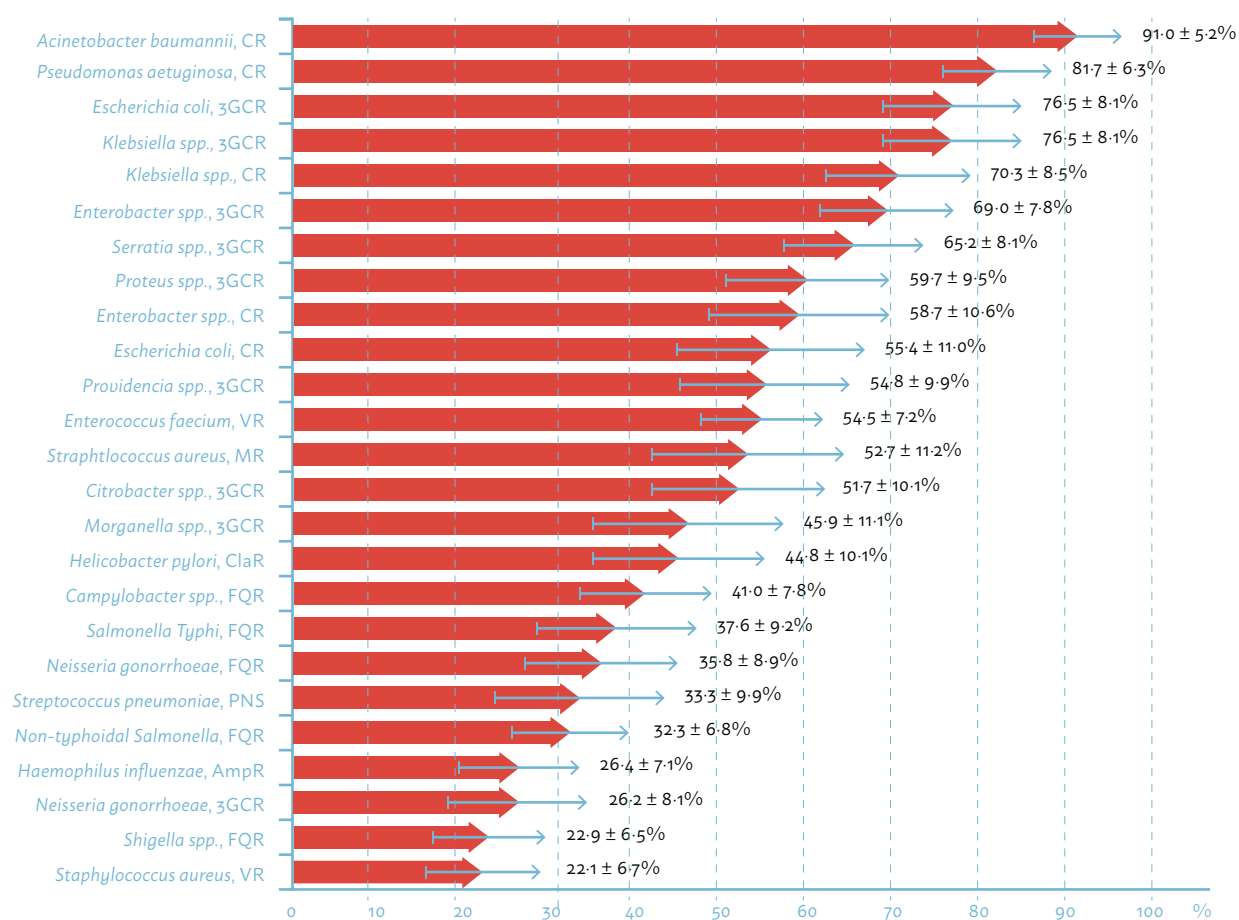
Community level

- *Neisseria gonorrhoeae*, fluoroquinolone-resistant
- *Salmonella spp.*, fluoroquinolone-resistant, 3rd generation cephalosporin-resistant
- *Staphylococcus aureus*, methicillin-resistant
- *Streptococcus pneumoniae*, reduced susceptibility to penicillin and macrolides
- *Streptococcus pyogenes*, reduced susceptibility to macrolides
- *Shigella spp.*, fluoroquinolone-resistant
- *E. coli*, fluoroquinolone-resistant and 3rd-generation cephalosporin-resistant

Hospital level

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant and polymyxin-resistant
- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant

Figure 1. WHO Critical-priority non-tuberculosis bacteria list to guide research and development of new drugs. Final ranking (mean weight and standard deviation).



Source: http://www.who.int/medicines/areas/rational_use/PPLreport_2017_09_19.pdf.

AmpR: ampicillin-resistant, **CR:** carbapenem-resistant, **ClaR:** clarithromycin-resistant, **FQR:** fluoroquinolone-resistant, **MR:** methicillin-resistant, **PNS:** penicillin non-susceptible, **3GCR:** third-generation cephalosporin-resistant, **VR:** vancomycin-resistant.

Antimicrobial misuse significantly increases:



» Allergic and adverse drug reactions



» Morbidity and mortality, in the community and in hospitals



» Length of stay for hospitalized patients



» Infections due to multidrug resistant pathogens



» Microbiota changes, including – but not limited to- *Clostridium difficile* infections



» Overall costs of medical care

Nathwani and Sneddon (4) summarized several facts affecting antimicrobial prescription in a 30% rule, as follows:

- » around 30% of all hospitalized inpatients at any given time receive antibiotics
- » over 30% of antibiotics are prescribed inappropriately in the community
- » up to 30% of all surgical prophylaxis is inappropriate
- » around 30% of hospital pharmacy costs are due to antimicrobial use
- » 10-30% reduction of pharmacy costs can be achieved by antimicrobial stewardship programs (ASPs)

PURPOSE OF THESE RECOMMENDATIONS

These recommendations are intended to:

- » Propose comprehensive and practical guidelines for national authorities and decision makers in Latin American and the Caribbean on the implementation of ASPs related to human health, and aligned with quality of care and patient safety.
- » Guide hospital managers, administrators and various health care workers (HCWs) in the creation and/or strengthening of ASPs to tackle antimicrobial resistance and implement cost-effective interventions related to antimicrobial stewardship (AMS), taking into consideration challenges and opportunities present in Latin America and the Caribbean.

SCOPE OF THESE RECOMMENDATIONS

These recommendations address ASPs in the context of acute care hospitals and ambulatory primary health care centers (PHC). Long term care facilities and nursing homes will not be covered. Although all antimicrobials fall under the supervision of the ASP, antibiotics are the most frequently used, and this drug class will be the primary focus of these recommendations.

1.2. Background

Gabriel Levy Hara, Hospital Carlos G. Durand, Buenos Aires, Argentina

Limited information is available on the prevalence of antimicrobial resistant pathogens (5) in low to middle income countries. However, in Latin America, resistance to third-generation cephalosporins in *Escherichia coli* isolates is increasing (e.g., around 60% in many Mexican hospitals), and fluoroquinolones (around 60% in many hospitals in Colombia, Mexico, and Peru). Resistance to third-generation cephalosporins in strains of *Klebsiella pneumoniae* has also been documented (e.g., 75% in Peru) (5,6).

Studies on antimicrobial consumption are scarce in Latin America and the Caribbean. Wirtz et al. (7) found an increasing trend in the use of most classes of these drugs in many countries between 1997 and 2007. Observational studies estimated that misuse of antibiotics by health care providers in the Region is around 50% (8), and patients' self-medication, between 20% and 40% (8,9). On the other hand, there are no regional studies on antimicrobial use in hospitals; there is, therefore, an urgent need to advance current knowledge of antimicrobial

prescribing and consumption, both in community and acute care hospital settings. Standardized systems and indicators are needed at different health care levels to promote benchmarking, to guide policy-making, and to implement effective interventions to change antimicrobial use behaviors and sustain them in the long run.

WHAT IS AN ANTIMICROBIAL STEWARDSHIP PROGRAM?

According to the Infectious Diseases Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society (PIDS) ⁽¹⁰⁾, antibiotic stewardship consists of coordinated interventions designed to improve and measure the appropriate use of antibiotic agents by promoting the selection of the optimal drug regimen, including dosing, duration, and route of administration. Despite the ongoing debate regarding the use of the terms antibiotic and antimicrobial stewardship, the present recommendations -in line with WHO- adopt AMS, given that the use of other drug classes, such as new antifungals, might also need to require efforts to promote their appropriate use.

ASPs deal with initiatives to implement evidence-based interventions that optimize the use of antimicrobials, while minimizing the development of resistance. Such initiatives cover, but are not limited to, regulatory and policy interventions and guideline development. From a practical standpoint, ASPs might be seen as the appropriate and rational set of actions aimed at using antimicrobials in a way that ensures sustainable access to effective therapy, while limiting adverse effects ⁽¹¹⁾.

PURPOSE AND BENEFITS OF ANTIMICROBIAL STEWARDSHIP PROGRAMS

The purpose of ASPs is to improve the use of antimicrobial agents in every clinical aspect ^(12,13), i.e., correct drug selection, including adequate/balanced spectrum; administration at the right time, in the right dose, by the appropriate route, and at proper time intervals. Increasingly, evidence indicates that ASPs improve the quality of patient care and patient safety, optimize the treatment of infections, and reduce adverse events associated with antibiotic use (Box 1) ^(14,15,16,17,18).

ANTIMICROBIAL STEWARDSHIP PROGRAMS IN LATIN AMERICA

Hospital antimicrobial stewardship programs are relatively new in Latin America when compared to other regions, such as Europe and the United States of America. In recent years, some hospitals have begun ASPs in several countries, in most cases, as individual projects, and not in answer to official national policies ⁽¹⁹⁾. Between March and September 2012, an international survey on antimicrobial stewardship in hospitals

BOX 1. BENEFITS OF ANTIMICROBIAL STEWARDSHIP PROGRAMS



» Improved clinical outcomes



» Reduced antimicrobial consumption



» Reduced associated treatment cost



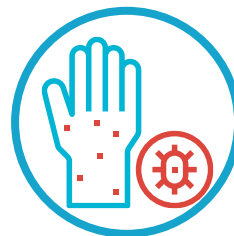
» Improved therapy and prophylaxis prescription



» Reduced treatment failure and mortality



» Reduced hospital rates of *Clostridium difficile* infection (CDI) and other health care associated infections



» Reduced antibiotic resistance among common nosocomial pathogens (e.g., methicillin-resistant *Staphylococcus aureus* (MRSA) and gram-negative bacteria)



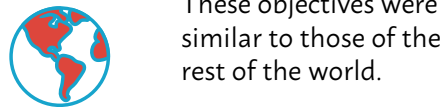
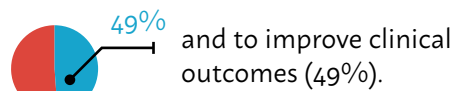
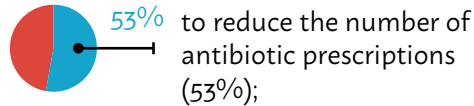
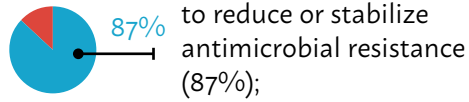
» Reduced drug-related side effects and drug interactions

was conducted jointly by the European Society of Clinical Microbiology's Infectious Diseases Study Group for Antimicrobial Stewardship (ESCMID/ESGAP) and the Antimicrobial Stewardship Working Group of the International Society of Antimicrobial Chemotherapy (ISC) (20). Sixty-seven countries in six continents participated. Of 660 responses, 103 were from Central and South America. Standards for AMS in hospitals varied from country to country. Overall, 46% of hospitals already have an ASP, compared to 58% in the rest of the world, and 66% and 67% in Europe and North America, respectively). The study's main results are summarized in Box 2.

Some interventions have been developed at the community level, including mandatory prescriptions for antibiotic pharmacy sales. To curb antibiotic self-medication, Chile in 1999 (21), Colombia in 2005 (22),

BOX 2. MAIN RESULTS OF AN INTERNATIONAL SURVEY OF HOSPITAL ANTIMICROBIAL STEWARDSHIP PROGRAMS

» Main objectives of asps were similar in all countries:

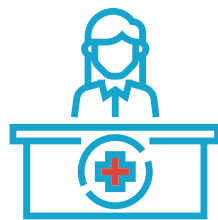


» Brazil, Chile and Colombia had larger numbers of hospital ASPs in place.



» Median number of **3 years** with ASP in place.

» Average number of dedicated hours per week of members of the AMT showed some differences when compared to global results:



a). Antimicrobial or infectious diseases pharmacist: mean 9

hours a week of dedicated work vis-à-vis a world mean of 18 hours



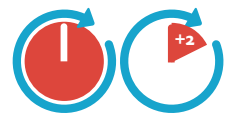
b). Infectious diseases doctor: mean 12 hours a

week vis-à-vis a world mean of 10 hours



c). Clinical microbiologist: mean 7 hours a

week vis-à-vis a 9 hours world mean



d). Nurses: mean 14 hours a week compared to a world mean of 6 hours

Source: Howard P, Pulcini C, Levy Hara G, West M, Gould IM, Harbarth S, Nathwani D. An international cross-sectional survey of antimicrobial stewardship programmes in hospitals. *J Antimicrob Chemother* 2015;70: 1245–1255.

and Brazil and Mexico in 2010 (23,24) introduced policies that were successful in reducing antibiotic consumption. In Mexico, a 12% decrease was attained, largely in penicillin consumption. Once the regulation was implemented, high seasonal fluctuation of penicillin consumption also diminished, reflecting a previously inadequate use of antibiotics to treat viral acute respiratory tract infections, typical of antibiotic misuse. Furthermore, after applying the regulation, increments in bacterial infection-related hospital admissions were not detected, which had been a feared consequence of the intervention. Enforcing laws that restrict antibiotic sales to prescription only in other countries, as well as reinforcing regulations over time, together with the development of more comprehensive measures to promote adequate use of antibiotics in the community, remain a challenge in Latin America (25).

1.3. Leadership and Accountability at National Level

Sylvia Hinrichsen, Center for Health Sciences, Universidade Federal de Pernambuco, Recife, Brazil

Antimicrobial stewardship programs are part of the WHO Global Action Plan on Antimicrobial Resistance (26) and the PAHO Regional Action Plan (27). In fact, Objective 4 of the WHO Global Action Plan includes recommendations for optimizing the use of antimicrobial medicines in human and animal health. The same objective specifically addresses the need for Member States to establish stewardship programs “that monitor and promote optimization of antimicrobial use at national and local levels in accordance with international standards in order to ensure the correct choice of antimicrobials at the right dose, based on evidence” (26).

Implementation of ASPs is a global strategy that needs strong leadership from all stakeholders, including patients, health care providers (in hospital and outpatient services), scientists, the health insurance and pharmaceutical industries, the agriculture/livestock sector, sewage and garbage facilities, and regulatory institutions. Specific financial support is also required to fund ASPs and to provide sustainability. Preferably, said funding should come from government sources (4,28).

The national core elements of ASPs in hospital and primary health care should cover governance, with its components and organizational chart; diagnostic stewardship; a regulatory framework; and leadership.



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**Propose comprehensive
and practical guidelines for
national authorities and
decision-makers in Latin
American and the Caribbean
on the implementation of ASPs
related to human health, and
aligned with quality of care
and patient safety.**

In 2014, the United States Centers for Disease Control and Prevention (CDC) published *Core Elements of Hospital Antibiotic Stewardship Programs*, to assist hospitals in effectively implementing antibiotic stewardship. The elements are (13):

- » **Leadership commitment:** Dedicating necessary human, financial and information technology (IT) resources.
- » **Accountability:** Appointing a single leader responsible for program outcomes. Experience with successful programs show that a physician leader is effective.
- » **Drug expertise:** Appointing a single pharmacist leader responsible for working to improve antibiotic use.
- » **Action:** Implementing at least one recommended action, such as systemic evaluation of ongoing treatment needs, after a set period of initial treatment (i.e. “antibiotic time out” after 48 hours).
- » **Tracking:** Monitoring antibiotic prescribing and resistance patterns.
- » **Reporting:** Regular information on antibiotic use and resistance to doctors, nurses and relevant staff.
- » **Education:** Educating clinicians about resistance and optimal prescribing.

Leadership support is also critical for the success of ASPs in hospitals, which may include different aspects (13), and could apply to the national, regional and local levels, including:

- » Formal statements that the facility supports efforts to improve and monitor antibiotic use
- » Incorporation of stewardship-related duties in job descriptions of members of the antimicrobial stewardship team or AST (leaders, pharmacists, microbiologists, etc.) and annual performance reviews
- » Ensuring sufficient time, based on hospital complexity, to contribute to stewardship activities of staff from relevant departments
- » Training and education support for all health care workers involved in antimicrobial utilization
- » Ensuring participation from various groups, such as patient safety and quality of care, that can support stewardship activities
- » Financial support, as it greatly increases the capacity and impact of an ASP

Early identification of potential barriers and using mitigation strategies to address them in the ASP plan are key to the future success of the program. Investing in dedicated staff time is an important step in hospital leadership to build a solid and sustainable ASP. There ought to be a clear vision of the need for and advantages of this step, among the latter, anticipated cost reductions associated with a decrease in excessive use or misuse of antimicrobials, adverse drug events (toxicity and resistant infections), and reduced length of hospital stay (29).

Cost saving interventions may include: a) switch of intravenous to oral therapy; b) restriction, supervision and monitoring of high-cost antibiotic use; and c) reduction in overall use. In estimating cost avoidance, improved patient outcomes can be measured in: a) decreased length of stay; b) decreased incidence of *C. difficile* infections; c) decreased antibiotic resistance; and d) decreased incidence of toxicity.

ASPs usually pay for themselves through savings in both antibiotic expenditures and indirect costs (30); consequently, national authorities may consider providing financial support to begin program implementation. This support could be either included in the annual public health budget, or provided through special funding. These funds should be allocated, at a minimum, to the payment of staff involved in program implementation (physicians, pharmacist, microbiologist, other), and to build and sustain minimum required resources, such as a clinical microbiology laboratory (CML), and a basic information technology network.

One potential strategy for ministries of health (MOH) is to fully support the organization of ASPs in all third-level hospitals of every region or province throughout the country. As those programs advance and become self-supporting, MOH funds may be derived to other institutions of the same region or province.

The first step in implementing an ASP is to identify a program leader who will be responsible for program outcomes. Physicians – ideally, infectious diseases specialists – have been highly effective in this role. A pharmacy leader with previous training in infectious diseases, antimicrobials and/or antimicrobial stewardship could co-lead the program (see section II.2).

Although the implementation of a successful ASP is a challenge in any health care setting, non-academic and rural hospitals present their own set of difficulties. It is advisable, therefore, that ASPs follow a stepwise process of implementation of initiatives and principles that respond to institutional needs. Larger facilities have achieved success by hiring full-time staff to develop and manage ASPs. Smaller hospitals could count on part-time off-site specialists in different subject areas. Additional expertise acquired through joint multi-hospital collaboration or by remote consultation (e.g., telemedicine) helps the establishment of regional and local networks closely coordinated with the national leadership (13,30,31). Such networks could use strategies like a) virtual

meetings with brief presentations of different aspects of the program and group discussions, for example, how to launch an ASP; human and material resources needed; training of team members; knowledge diffusion; selection and adaptation of clinical guidelines; and b) discussing common barriers and ways to overcome them, including mutual assistance among network members.

I.4. Antimicrobial Availability

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It is pivotal for any ASP – whether at hospital or primary care level- to have uninterrupted stocks of relevant antimicrobials easily available for prescribers. This need for continued availability of essential drugs includes both newer or relatively newer antimicrobials, as well as older – and often forgotten – ones. In fact, even though most guidelines frequently recommend older antimicrobials as first line of treatment, those drugs are not universally marketed or available (32). This may seriously impact antibiotic prescribing, and foster over prescription of newer and broader spectrum drugs, with worse results. Such alternatives may also be less effective, may have more adverse effects, and may drive the selection of resistant strains (32).

Any initiative directed at rationalizing the use of antimicrobials, like ASPs, must address drug selection, procurement and distribution issues. A regularly updated list of essential drugs ensures stable supplies. Their use, based on clinical guidelines developed by consensus with stakeholders, should reduce prescription of unnecessary antimicrobials and prevent their inclusion in the hospital's list.

The WHO's 2017 Essential Medicines List (33) classifies antimicrobials in three categories:

1. **Key Access:** These are first line antimicrobials that should be available at all times to treat a wide range of common infections.
2. **Watch:** These are antimicrobial agents designated as first or second line of treatment for a small number of less common infections or when alternatives are necessary in allergy cases. Due to their nature, attention should be paid to their indication and impact on antimicrobial resistance.
3. **Reserved:** These are antimicrobials of last resort, used only in the most severe circumstances, when all other alternatives listed in the key access and watch categories have failed.

Many factors may lead to antimicrobial shortages, both related to demand (e.g., changes in demand, budget changes, import limitations), as well as supply (e.g., high registration costs and small market size for older drugs, transportation issues, quality deficiencies, and scarcity of periodical structured inventories). Another concern is the lack of awareness or low prioritization of shortages by health authorities.

Regarding procurement and distribution, the report of the International Summit on Medicine Shortage hosted by the International Pharmaceutical Federation and held in Toronto in 2013 ⁽³⁴⁾ defines the causes of shortages and their solutions. It also looks in detail at demand and supply aspects of all medicines. The Summit issued six recommendations that Latin American and Caribbean countries should adopt regarding antimicrobials:

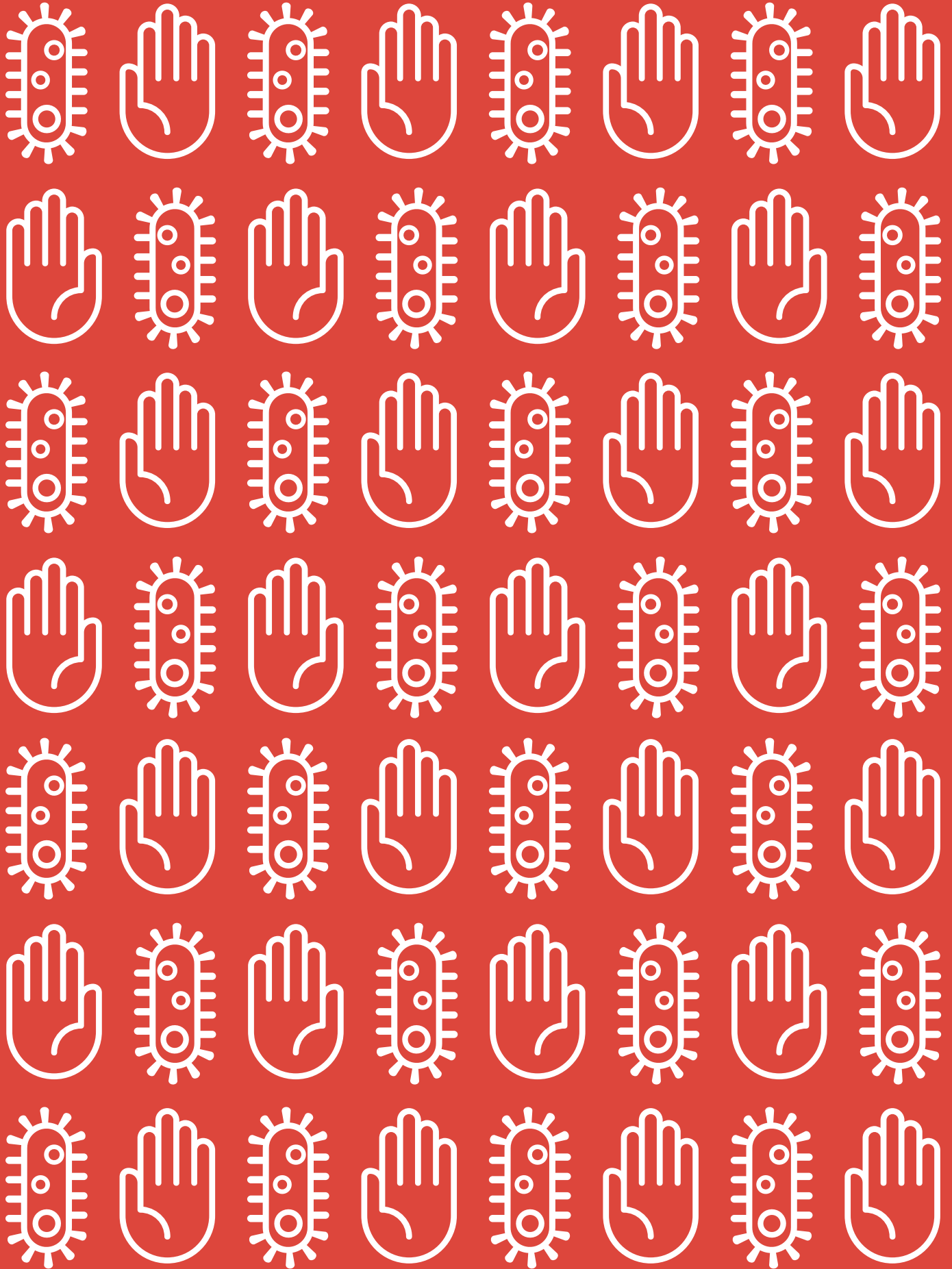
- » Timely provide information about shortages;
- » Develop a list of critical antimicrobials;
- » Providers must project availability;
- » Facilitate all regulatory and bureaucratic processes throughout the supply chain;
- » Develop mitigation strategies in case of shortages;
- » Ensure high-quality control standards for antimicrobials;

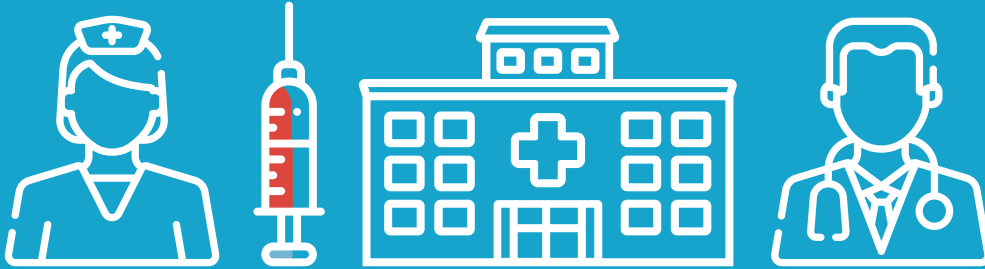
In terms of antimicrobial medicines availability, the Region should consider adopting the following recommendations:

- a. Develop and publish status reports that provide timely and complete information on current shortages of antimicrobials, and explain their reasons, anticipated duration, and contingency plans to address them. Reports should be widely accessible, and may involve the ministries of health, regulatory authorities, professional and industry associations, and other stakeholders.
- b. Develop a list of critical antimicrobial drugs based on the local infectious diseases epidemiology, drug availability, production complexity, the geographical distribution of health-care facilities, treatment indications, and availability of substitute agents. This would be a task for the Ministry of Health, regulatory authorities, and professional and industry associations.
- c. Strive for high-quality procurement processes that include accurate supply projections, and consistent communications among procurement agencies and manufacturers regarding availability.
- d. Remove unnecessary variability of regulatory practices within and among countries, and keep all regulatory processes transparent. Manufacturers are encouraged to share non-competitive audits of suppliers and contractors to enable coordinated responses

- e. Establish a national supervisory body charged with sharing demand and supply information on antimicrobials within their jurisdiction, being it national or subnational, depending on the country.
- f. Develop mitigation strategies to address antimicrobial shortages, which could address topics such as buffer stocks and stockpiles, contingency planning, pandemic planning, and capacity redundancy, as appropriate to national needs.
- g. Ensure that antimicrobials meet vigorous quality control standards.

Several of these recommendations are part of mid- to long-term strategies. Countries are encouraged to adopt short term solutions, such as defining acceptable antimicrobial alternatives to first line drugs in the event of shortages, based on clinical guidelines. It is important to establish national and local dynamic and functional networks (for example, for hospitals in the same city) to enable the exchange or borrowing of antimicrobials when needed.





Part II

Antimicrobial Stewardship
Programs in
Hospitals – Implementation

II.1. Organizational Aspects

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The ASP is widely accepted as an efficient strategy to combat the growing threat of antimicrobial resistance. There is also general agreement that antimicrobial stewardship is a team effort that must involve all health care workers in the continuum of care. ASPs may vary by health care institution, therefore, flexible and tailored approaches to local needs are essential. The elements presented here are not intended as a mandatory checklist, but rather, a summary that may help hospitals ensure that each core component of the program is in place (4, 13, 28, 31, 35, 36).

Leadership commitment by hospital authorities and boards of trustees is important to obtain resources in support of ASPs. Leadership commitment from the chief medical officer (CMO), pharmacy director, and nurse leaders can facilitate the engagement of physicians, pharmacists, infection prevention and control staff, microbiologists and nurses to implement antimicrobial stewardship initiatives that create strong and sustainable programs. Each health care institution needs to put in place strategies to support the creation, implementation, development and control of outcomes of the ASP, as shown in Table 1.

TABLE 1. MAIN STRATEGICAL ELEMENTS OF AN EFFECTIVE ANTIMICROBIAL STEWARDSHIP PROGRAM (ASP)

COMPONENT	STRATEGY
LEADERSHIP	Designate an antimicrobial stewardship team leader to report on the outcomes of ASP implementation.
CONSISTENT POLICY	Approve a policy for the creation and/or expansion of the ASP that includes all core and key support members.
INTEGRATE ACTIVITIES	Ensure ASP is consistent with ongoing quality improvement and/or patient safety efforts in the hospital.
REPORTING	Periodically share information on antimicrobial stewardship interventions and outcomes with the facility's leadership, and at board meetings.
FORMAL BOARD APPROVAL	Issue a statement on the importance of the ASP as part of hospital's annual reports.
DISSEMINATION WITHIN FACILITIES	Inform all providers and patients of the hospital's commitment to improve antibiotic use (e.g., flyers and posters). Clarify the role of staff involved in antimicrobial stewardship.
TRAINING	Support online or in-person training programs for members of the antimicrobial stewardship team, and for prescribers at different levels.

In resource-restrained settings, key components of the antimicrobial

stewardship model may be implemented in step-by-step fashion, and progressively upscaled. Some suggested initial components are:

1. Formalization of measurable goals for the hospital. For example, determining the proportion by which antibiotic consumption will be reduced, and quality improvements in the use of antibiotics.
2. Establishment of a multidisciplinary AST (see section 11.2) that includes prescribers to ensure their endorsement of the program.
3. Through local and national training workshops, developing and launching a toolkit that includes standardized templates and indicators to measure and record performance.
4. Recording specific antimicrobial stewardship activities implemented by various members of the AST in a given period in targeted health care units. This could begin in intensive care and high care units, and in selected wards thereafter.
5. Providing periodic verbal and written feedback on progress and barriers to prescribers.

NETWORK OF ANTIMICROBIAL STEWARDSHIP PROGRAMS

Preparing for and implementing ASPs is a hard and long-lasting process. Barriers arising from the scarcity of human and material resources are not exclusive of low- and middle-income countries. This creates the need for collaboration within the health care system to make this synergistic process successful. One useful strategy might be to begin implementation in main regional or city hospitals, due to their higher complexity, and usually higher antimicrobial consumption. Once said programs are organized and expanding, the experience can be expanded to lower complexity hospitals, by means of: a) workshops aimed at current and future ASP leaders of all participating hospitals; b) hospital visits (experienced AST members visit hospitals initiating programs, and vice-versa); c) periodic virtual meetings to discuss main issues, progress and barriers; and d) training for antimicrobial stewardship, among others.

This network could remain in place beyond the implementation phase. In fact, hospitals would need to provide and receive mutual support in several areas, such as communication and containment of emerging multidrug resistant pathogens, referral for specific diagnostic tests, sharing medications when lacking in a given hospital, etc. The need for accountability at the national, regional, and local levels cannot be emphasized enough, as it is pivotal to the creation and sustainability of effective networks.

11.2. Members of the Antimicrobial Stewardship Team

Gabriel Levy Hara, Hospital Carlos G. Durand, Buenos Aires, Argentina

Establishing a multidisciplinary AST with full administrative support is essential for a robust ASP. The team's composition should be adapted to the human resources available in each facility. Leaders – both hospital authorities and team members – may have to be creative when building a team and establishing a program, given the many barriers to the process. It would not make sense, therefore, to set a rigid team structure in this document. Rather, suggestions will be provided, mostly regarding the composition of the AST, as proposed in various international guidelines (4, 12, 13, 28, 37), stakeholders who should be core members, and those who should have a supporting role, depending on the circumstances.

Ideally, the AST should be under the direction or supervision of a physician, and include at least one member trained in antimicrobial stewardship. Alternatively, a pharmacist, a clinical microbiologist or a physician with antimicrobial management expertise could assume the team's leadership. The ASP would be enhanced by the inclusion of the patient safety and quality departments, as well as an infection prevention and control nursing specialist, information technology staff, hospital administration staff and physicians (such as hospitalists) from various institutional departments. Even if these professionals are scarce, an ASP must be implemented (28,37).

CORE MEMBERS



Physicians. Ideally, the coordinator should be an infectious diseases specialist; this, however, is not mandatory. The physician team leader, working in close collaboration with a pharmacist, should be involved in all phases of the ASP's development. Antimicrobial stewardship activities should be clearly defined, and independent from responsibilities that might distract from them, such as patient consultations, participation in other hospital committees, or non-antimicrobial stewardship activities.



Pharmacists. When resources are available, a pharmacist formally trained in AMS, antimicrobials or infectious diseases must be a core member of the AST. However, since these specialized professionals are not widely available in Latin America and the Caribbean, a pharmacist interested in improving the use of antimicrobials can be identified by the leader, trained in basic aspects of antimicrobial stewardship; and provided with further in-service training in the field.

Pharmacists can be involved in multiple tasks as part of an ASP, as many strategies are pharmacy-driven (see section 11.3). Among them, the pharmacist should work jointly with the infectious diseases team in the development of clinical practice guidelines, and actively follow prescribers' adherence. Political commitment and support from various hospital departments' heads is critical to incorporate a dedicated pharmacist in these quality improvement efforts.

Microbiologists. Ideally, these professionals should have some training in clinical microbiology. The full role of the clinical microbiology laboratory (CML) will be developed in depth in section 11.5. Nonetheless, the following are some examples of the contributions that microbiologists can make to the ASP:

- a. Daily report to prescribers regarding results of clinical specimen testing (i.e., direct examination, cultures and susceptibility tests).
- b. Updated information on local/hospital resistance patterns as per antibiogram in various hospital units. This input helps the rest of the AST develop or modify clinical practice guidelines; to assess which antimicrobials should be more closely controlled; and to determine specific monitoring strategies, including bacterial prevalence and resistance patterns.
- c. The implementation of selective reporting to the AST could initially drive the use of drugs with lower resistance pressure and/or cost. This strategy must have the agreement of hospital authorities and the entire AST to prevent challenges to its implementation.

Hospital authorities must provide access to a well-functioning laboratory with microbiology professionals to ensure the success of an ASP. When outsourcing laboratory services, timely and appropriate transportation of clinical specimens to the selected CML must be guaranteed. It is also critical that offsite laboratories provide daily updated information, and be easily accessible to communicate with prescribers.

General practitioners. These professionals could also be leaders of the AST, given their increasing presence in inpatient care, their frequent use of antibiotics, and their commitment to quality improvement. When the institution does not employ infectious diseases specialists, interested hospitalists with previous training in antimicrobials (generally, internal medicine or intensive care physicians) may assume leadership of the program.

Irrespective of who the AST leader is, it is essential that the team includes one representative from each hospital key unit. Without committed hospitalists, the ASP could fail. In fact, the team leader or infectious diseases physicians - despite their enthusiasm and commitment - would not be able to cover all units and provide recommendations on daily antimicrobial use. The selection of key units will depend on the quality and quantity of antimicrobial consumption, which may vary from one facility to another. However, the most commonly selected are intensive care (ICU) and internal medicine units, and emergency and surgery departments. Since physicians are the actual prescribers, their inclusion in the team will



... Many successful prescription-based strategies can be implemented in hospital ASPs. However, no single template fits all hospitals. In fact, one key feature of successful ASPs is their potential to adapt to the specific characteristics and circumstances of every hospital setting ...



facilitate dissemination of and adherence to antimicrobial stewardship guidelines. Every representative should generate discussions on antimicrobial prescriptions in his or her unit, encourage participation in the development of guidelines, and collaborate in the implementation of antimicrobial stewardship strategies. Representatives might be selected by unit heads, in agreement with the AST leader, among those staff more interested in and committed to this issue. Frequently, younger colleagues interested in antimicrobial use are ideal team members.

SUPPORTING MEMBERS

The work of stewardship program leaders is greatly enhanced by the support of other key groups, such as:

Infection prevention specialists and hospital epidemiologists.

Epidemiologists are not usually part of the staff of hospitals in Latin America and the Caribbean. Consequently, participation in the AST falls on some members of the infection prevention and control (IPC) committee, i.e., infection prevention specialists. Interaction between team members and the IPC is needed to update infection prevalence statistics and trends throughout the facility, and to ensure that necessary precautions to prevent the spread of multidrug resistant organisms are in place. The IPC committee usually can improve communications between the clinical microbiology laboratory and clinicians. In addition, hospital epidemiologists, when available, can lend their expertise in data auditing, monitoring, and reporting.

Nurses. In many countries, nurses are included in antimicrobial stewardship activities (20, 28, 31, 37), given that these professionals spend most of their time by their patients, and interact with many other clinicians. Some interventions where nurses are essential include:

- » Facilitating compliance with infection prevention and control measures
- » Ensuring the performance of cultures prior to starting antibiotics
- » Recognizing any overuse or wrong doses of antimicrobials
- » Detecting adverse events that are infusion - or drug-related
- » Ensuring the accuracy of patients' allergy history

Information technology staff. This area is critical to integrating stewardship protocols into the existing workflow. As will be described in sections 11.3 and 11.5, below, many interventions need IT support. In the beginning phases of the program, IT is important to collect basic

information on unit-specific antimicrobial consumption and hospital data (e.g., admissions, patients-day, days of therapy, or defined daily doses). Later, as the ASP matures, other indicators or measures, such as medication requests by unit and microbiology results, as well as linking information and protocols at the point of care, and clinical decision support could be progressively implemented.

Quality improvement staff. The prudent use of antimicrobials falls under the quality improvement umbrella, as it impacts patient safety. If there is such a department in the hospital, its representative should be part of the antimicrobial stewardship team.

In summary, establishing an AST is a must. With limited resources, the architects of the team will need to be creative and use readily available hospital resources. With some degree of expertise in antimicrobial stewardship and on-the-job training, it is possible to begin implementation, without having to wait for a full team to be available. Once the team begins to work and authorities realize the advantages of having such a team, it will be easier to obtain stronger commitment from management to facilitate the team's expansion.

11.3. Recommended Prescription-Based Strategies for Hospital ASPs

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Many successful prescription-based strategies can be implemented in hospital ASPs. However, no single template fits all hospitals. In fact, one key feature of successful ASPs is their potential to adapt to the specific characteristics and circumstances of every hospital setting, including available human and material resources (see section 11.2, above).

In this section, several prescription-based strategies will be summarized. Initially, hospital authorities together with the AST should select the strategies that could better fit their institution, and visualize a program implementation as a step-by-step dynamic process. For example, in settings with a small AST and no prior stewardship experience, it would be necessary to establish a pre-prescription authorization strategy for some antimicrobials, accompanied by targeted education initiatives. Once the *stewardship spirit* is better spread throughout the institution and the stewardship team is stronger, preauthorization might no longer be necessary. The latter strategy could progressively be turned into post-prescription audit and feedback. A timely adoption of a combination of strategies is imperative for the ASP's success.

Following are the Regional PAHO/FIU recommendations on the most relevant and applicable prescription-based strategies for hospital settings.

A. PRESCRIPTION PRACTICES

1. ANTIMICROBIAL PRESCRIBER SELF-ASSESSMENT AFTER 48-72 HOURS OF TREATMENT

It is important to instill the idea that antimicrobial care is the responsibility of all hospital units, and not exclusively of the AST. Therefore, this strategy involves all hospital prescribers, a key factor for the program's socialization. All prescribers from every hospital unit should reassess antibiotic prescriptions after 48 to 72 hours of onset of treatment (13, 38). Such a review should determine whether a written antibiotic plan is available (drug name, dose, route, interval of administration, and planned duration); serve to confirm the diagnoses, and adapt the treatment to microbiological results; and switch from intravenous to oral administration. Checklists can facilitate and enhance compliance with this strategy.

Once microbiological results are available, empirical antibiotic treatment should be streamlined accordingly, by choosing the most active drug(s) with the least toxicity, the narrowest spectrum, and the lowest cost (39). As for all strategies in the ASP, prescriber education is a cornerstone of this intervention (See section III.3). Moreover, to continuously feed this practice, it would be ideal to combine the self-assessment with a post-prescription review (see below), as additional training and feedback.

2. PRESCRIPTION BY AUTHORIZATION

Certain antimicrobials could be restricted to ensure their prescription is reviewed by antibiotic experts prior to therapy administration. Drugs in this category should be agreed upon by hospital authorities, the AST and unit heads, to reduce frequent opposition to this sort of intervention. Antimicrobials requiring preauthorization could be selected based on spectrum, impact on the hospital's biota, cost, or associated toxicities (13). Use of restricted antimicrobials may be limited to certain indications, prescribers, services and/or patient populations.

Preauthorization requires well-trained and dedicated staff readily accessible to prescribers, and can be obtained in writing or with computer support. This strategy significantly improves antimicrobial use, especially during the first semester of ASP operations. In fact, a Cochrane review (14) showed that, compared to post-prescription strategies, restrictive interventions had greater impact on prescriptions in the first months, and microbiological improvements by the sixth month; these differences disappeared on the 12th and 24th month, respectively. The main disadvantages of restrictive interventions are: a) delays in initiating appropriate treatment; b) prescriber opposition due

to lack of autonomy; and c) the risk of increasing resistance to essential drugs misused to avoid the authorization process (e.g., piperacillin/tazobactam to avoid requesting authorization for carbapenems). Also, the long-term beneficial impact on resistance has not been established (40).

A friendlier approach to the preauthorization strategy is to allow the attending physician the use of the drug pending the approval by the AST after the first 48 to 72 hours of treatment. This would give prescribers more freedom and the team more time to review and discuss the antimicrobial regimen. This strategy, when combined with a strengthening of IPC measures and education, could be beneficial during the first phase of implementation of the ASP, or as part of a multiphase response to high burden hospital use of certain antimicrobials. Once the first phase is over and the AST is stronger, most or all antimicrobials could be free from restrictions, and the review could take place as part of a post-prescription strategy.

3. POST-PRESCRIPTION REVIEW

The post-prescription review, also known as audit and feedback, may be prospective or retrospective.

Prospective (real-time) feedback is performed during scheduled joint ward rounds with medical staff and residents, with discussions of prescribed antibiotics. The review should follow institutionally agreed policies, i.e., affect all or just broader spectrum drugs, those with higher risks of side effects, and/or those of higher cost. The AST could suggest treatment changes verbally or in writing. Clinical aspects, date of initiation of the treatment, patient's outcome, response to therapy, microbiological results (if available), safety of the treatment, and possibilities of de-escalation or change of administration route (intravenous to oral), and expected duration are discussed. Importantly, both staff physicians as well as residents/head of department may be present, due to several reasons (e.g., senior colleagues have more resistance to changes; junior colleagues would increase their knowledge to support those changes and more elements to discuss, etc.).

The frequency of rounds will depend, mainly, on human resources (e.g., size of the AST), and the burden of antimicrobial consumption (quantity and quality) in a given ward or unit. For example, ICU rounds may take place around three times a week, compared to once or twice a week in surgical units.

When possible, pharmacists and microbiologist should join these rounds, so that all elements affecting every treatment may be addressed, such as clinical outcome, laboratory results, spectrum of current treatment and possible adjustments, toxicity and drug interactions.

All heads of unit must understand that it is the unit's medical staff who have responsibility for obtaining updated microbiology test results (Gram stains, cultures, antibiograms, and other) through daily communication with the clinical microbiology laboratory, to expedite therapy adjustments.

Post prescription interventions offer some advantages (40). After 48 to 72 hours of antimicrobial treatment, more clinical and microbiology data will be available for therapeutic decision-making. These interventions can be performed even when human resources are scarce; also, the approach is certainly less restrictive than pre-prescription authorization, and it has the additional advantage of providing prescribers continued training. It is critical to look for diagnostic and therapeutic agreements with unit heads and staff during ward rounds; if the AST attempts to impose the desired changes, prescriber compliance will not be better than with pre-prescription strategies.

Retrospective audit with feedback involves the assessment of antibiotic therapy in hospitalized patients by pharmacists and/or nurses. They compile audit data for a defined period and provide feedback to the prescribers pointing out where antibiotic antimicrobial therapy is considered suboptimal. This provides an opportunity for clinical personnel to discuss their own prescribing, and to identify priority areas for change might be improved. Depending on the local scenario, the AST could define which antimicrobials will be audited, as for example, antibiotics whose consumption has increased significantly over time; or with more potential to induce resistance (e.g. fluoroquinolones, 3rd generation cephalosporins); or with broader spectrum (e.g. piperacillin/tazobactam, ticarcillin/clavulanate, carbapenems); or last line antibiotics (e.g. polymyxins, tigecycline, fosfomycin, linezolid); or those with higher cost, such as selected antifungals (e.g. lipid formulations of amphotericin, echinocandins, voriconazole and posaconazole).

B. PHARMACY-DRIVEN INTERVENTIONS

In addition to the above, pharmacists may directly implement other practices. Again, to prevent resistance from physicians, all affected parties (authorities, medical staff, AST members, etc.) ought to be in agreement. Evidence indicates that, as the ASP matures, this issue is progressively resolved, and pharmacists become an integral part of the medical care team (31).

In Latin America and the Caribbean, medicines are still frequently requested from the pharmacy by hospital wards in writing or electronically. This method is far from ideal, as it limits control over the appropriateness of prescriptions, and facilitates the accumulation of stocks. Getting the clinical pharmacist to pick up medication requests daily from treatment wards may be the first step in adding this essential specialty in AMS activities.

PHARMACISTS, IN AGREEMENT WITH PRESCRIBERS, MAY COLLABORATE IN VARIOUS TASKS, SUCH AS (4, 13, 31, 37, 39):



» Review requests for antimicrobials that require preauthorization.



» Provide feedback during multidisciplinary ward rounds.



» Detect unnecessary prescriptions while collecting medication requests from hospital units.



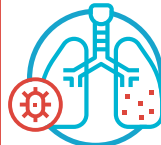
» Detect unnecessary prescriptions while collecting medication requests from hospital units.



» Dose adjustments in cases of organ dysfunction (e.g., renal adjustment).



» Dose optimization (e.g., adjustments based on therapeutic drug monitoring, therapy optimization for highly drug-resistant bacteria, tissue penetration, prolonged-infusion administration, loading doses).



» Detect drug interactions (e.g., antiretrovirals, antituberculosis drugs).



» Detect inappropriate treatment duration.



» Advice on pharmacokinetic/pharmacodynamic issues, quality requirements for antimicrobials procurement.

C. OTHER CLINICAL INTERVENTIONS

Based on specific issues detected during the implementation of the ASP, a variety of interventions may be appropriate. Usually, these are initiated once the program is on its way, and priority issues, such as overall antimicrobial consumption, pre and/or post-prescription interventions, surveillance of higher prevalence pathogens, have been addressed and are improving. These follow-up interventions can be classified in two groups:

- a. *Specific antimicrobial interventions:* One example is monitoring increases in consumption of certain drugs or those of broader spectrum or higher cost (carbapenems, linezolid, lipid formulations of amphotericin, echinocandins, voriconazole and posaconazole). This process could begin with a pharmacist's alert (if no preauthorization form is in place), followed by discussions between a member of the AST and the prescriber to review the case.



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... pharmacists may directly implement other practices. Again, to prevent resistance from physicians, all affected parties (authorities, medical staff, AST members, etc.) ought to be in agreement. Evidence indicates that, as the ASP matures, this issue is progressively resolved, and pharmacists become an integral part of the medical care team.

b. *Disease or condition-specific interventions:* When a frequent problem is detected via microbiology alert, ward rounds or retrospective audit, a specific intervention might be designed. For example, an increase in urine cultures referred to the laboratory could mean that asymptomatic bacteriuria is being overly screened and, potentially, overtreated. Another issue might be when and how to obtain respiratory samples from patients in mechanical ventilation, and the interpretation of their tests results. Common diseases, such as skin and soft tissue infections and community acquired pneumonia may also be good candidates for specific ASP interventions.

Another straightforward approach is to assess patients with positive blood cultures for specific pathogens. Patients can be identified through communication with the CML or through alerts from computerized surveillance systems. (41)

D. COMPUTER-SUPPORTED INTERVENTIONS

Computer support in hospitals is growing, although it varies significantly among institutions, cities and countries (41). Regarding its use in ASPs, applications can go from supporting basic needs (e.g., antimicrobial consumption database and bacteriologic surveillance by hospital unit), to more sophisticated clinical decision support systems. Many of the above strategies use computer support to detect increases in consumption of certain drugs, and, in some cases, preauthorization of restricted antimicrobials. Another easy strategy involving the hospital's pharmacy consists of time-sensitive automatic stop orders for surgical prophylaxis. Unless explicitly stated by the treating surgeon, the antibiotic is suspended after a 24-hour period, consistent with local guidelines. This strategy may be more useful in the event of pharmacy staffing shortages, where pharmacy clinical services may be limited (13, 19, 42). This method has also been used to control prescriptions of some antimicrobials, such as carbapenems and vancomycin. Importantly, this intervention might only work in the presence of other control mechanisms (i.e., when the AST is closely in touch with prescribers), to prevent unsafe or erroneous interruptions. Section II.6 of this document further describes the use of information technology and computer supported interventions.

Table 2 provides a summary of prescription-based antimicrobial stewardship tasks, by strategy and by degree of progress of the ASP.

TABLE 2. RECOMMENDATION ON PRESCRIPTION-BASED STRATEGIES, BY LEVEL OF DEVELOPMENT OF THE ANTIMICROBIAL STEWARDSHIP PROGRAM

STRATEGY	BASIC LEVEL	INTERMEDIATE LEVEL	ADVANCED LEVEL
ANTIMICROBIAL PRESCRIBER SELF-REVIEW	Record every antimicrobial prescription in clinical records and prescription charts daily. Record microbiological test results in clinical records daily.	Prepare written antimicrobial stewardship plan. Review of diagnoses. Record microbiology results. Plan for de-escalation, switch from intravenous to oral administration, and adjust treatment duration. Treatment adjustments.	Include checklists with all elements of the bundle (day of antimicrobials, microbiological results, review of diagnoses, plan for de-escalation, duration, etc.).
PRE-PRESCRIPTION AUTHORIZATION	Evaluate implementation: a. For some critical antimicrobials (carbapenems, vancomycin, polymyxins, tigecycline, fosfomycin, antifungals and newly introduced drugs) b. In some units with higher burden of use and/or difficult to control in this first stage.	If possible, depending on degree of consumption and success of other strategies, such as audit and feedback, evaluate reducing number of restricted drugs and/or limit the number of units affected.	When possible, evaluate suspending restricted drugs.
POST-PRESCRIPTION REVIEW	Begin ward rounds in units with higher burden of antimicrobial use, such as ICUs, internal medicine, hematological ward. Set ward rounds frequency based on antimicrobial stewardship team size/resources. Try to include a pharmacist (if available) from the beginning.	Increase frequency of rounds in critical areas, and progressively add new units (e.g., surgical specialties). Include pharmacists and microbiologist in rounds, if not already done.	Extend rounds to all hospital wards. Adapt frequency of rounds based on needs.
PHARMACY-DRIVEN INTERVENTIONS	If currently medication requests from the pharmacy use a form, change to clinical pharmacist picking up daily requests from hospital units. Begin with units with higher burden of antimicrobial use (e.g., ICUs, internal medicine, hematological ward). Alert staff and the antimicrobial stewardship team regarding doses, route of administration, duration, interactions, and duplications, when pertinent. Develop a database of antimicrobial consumption for all wards. Begin pharmacist's participation in ward rounds, for contributions regarding basic issues, such as dose optimization, adjustments, drug interactions, and other.	Increase the number of units in which clinical pharmacist participates. Increase clinical pharmacist's participation in ward rounds. Introduce indicators of antimicrobial consumption, and use different methods, depending on resources (e.g., defined daily dose or DDD/100 or 1,000 patients; days on therapy).	In close collaboration with the information technology department, progressively incorporate computer support. Introduce therapeutic drug monitoring, for example, for vancomycin and aminoglycosides.
OTHER INTERVENTIONS	Surveillance of a small number of antimicrobials suspected or proven to be excessively or inappropriately used.	Disease-specific interventions based on issues detected in the first phase.	Implement a wider variety of disease-specific interventions, when necessary.

11.4. Microbiology Laboratory, In-Hospital Communications and Surveillance Networks

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The clinical microbiology laboratory has a key role in developing and maintaining a successful ASP. Clinical microbiologists can make relevant contributions to the ASP through cumulative antimicrobial susceptibility tests reports; enhanced susceptibility reports with footnotes and comments; sampling and transportation advice; rapid diagnostic tests availability; provider education; and development of surveillance systems (43,44). This section is devoted to the concepts of diagnostic stewardship, basic requirements for a clinical microbiology laboratory, suggestions for reporting and communicating results to clinicians and infection prevention teams, and methods to develop reports that become part of a database of the national network of hospitals.

WHAT IS DIAGNOSTIC STEWARDSHIP?

According to the WHO, diagnostic stewardship refers to the “coordinated guidance and interventions to improve appropriate use of microbiological diagnostics to guide therapeutic decisions. It should promote appropriate, timely diagnostic testing, including specimen collection, and pathogen identification and accurate, timely reporting of antimicrobial susceptibility results to guide patient treatment”. The four principles of diagnostic stewardship are:

- » **Right test:** Choose the method that provides accurate and clinically relevant information for best patient care. Consider costs versus benefits.
- » **Right patient:** The methods used must respond to patient needs. Take into consideration age, risk factors, co-morbidities, travel abroad, etc.
- » **Right time:** The methods should provide results in a rational time frame to promote timely antibiotic decisions. The time frame should be consistent with severity and risk factors.
- » **Right cost:** Balance cost versus accuracy, speed and clinical impact. Do not consider test cost as an outcome. Consider length of stay and days of inappropriate therapy when assessing a specific method's cost.

The main objective of microbiological diagnostic stewardship is to deliver:

- » patient management guided by timely microbiological data to deliver safer and more effective and efficient patient care; and
- » accurate and representative AMR surveillance data to inform treatment guidelines, and AMR prevention and control strategies.

The preanalytical phase of microbiologic diagnosis is probably more important than the analytic phase. Adhering to best practices for specimen sampling and transportation to the clinical microbiology laboratory is strongly recommended (Table 3).

TABLE 3. RECOMMENDATIONS FOR CLINICAL SAMPLE COLLECTION AND TRANSPORTATION TO THE CLINICAL MICROBIOLOGY LABORATORY, BY SPECIMEN TYPE

SPECIMEN TYPE	RECOMMENDATIONS FOR SAMPLE COLLECTION AND TRANSPORTATION
BLOOD	Blood cultures should preferably be drawn before administering the first dose of antibiotics. Use 2% chlorhexidine-alcohol for skin disinfection. Other options include 70% alcohol or povidone iodine. In neonates, use 0.5% chlorhexidine-alcohol. Allow antiseptic to dry completely, and disinfect tube cap prior to injecting the blood. For adults, 20 to 30 ml of blood per culture set is recommended (for children, a smaller amount is required, adjusted by age and weight). Usually two sets of blood cultures (two tubes each) are enough, unless an endovascular source is suspected (i.e., central line infection or endocarditis). In such cases, consider 2 to 3 sets. For automated systems, follow manufacturer’s instructions. Transport samples at room temperature.
URINE	Generally, urine cultures should be performed only on symptomatic patients to avoid treatment of asymptomatic bacteriuria. Urine is prone to contamination by commensal flora. Patients should be instructed in how to collect midstream urine (“clean-catch” urine) in a sterile container to minimize contamination. If any delay is likely while transporting the specimen to the laboratory, the specimen should be refrigerated immediately after collection to reduce the risk of overgrowth by contaminating organisms. Alternatively, urine may be collected in containers with boric acid when transport delay is anticipated.
GENITAL SPECIMEN	Appropriate urethral and cervical discharge collection is essential to ensure that <i>Neisseria gonorrhoeae</i> can be isolated successfully to support a gonorrhea diagnosis and determine antimicrobial susceptibility. Each specimen should be correctly inoculated in culture or placed in the appropriate transport medium. If culture medium is directly inoculated at the clinic or bedside, the plates are placed in an 5% CO ₂ -enriched humid atmosphere (or candle jar) at 35°C to 36°C and transferred to the laboratory as soon as possible. If the specimen cannot be inoculated immediately onto the culture medium, the swabs should be inserted into a non-nutrient transport medium such as Stuart or Amies. These can be left at room temperature and transported as soon as possible to the laboratory. Isolation rates after specimen transport in a non-nutrient medium at room temperature (25°C) decrease after 24 hours.
STOOL	A stool specimen should be collected in a clean specimen container and transported at room temperature to the CML, ideally within 2 hours. Local standard operating procedures for stool specimen collection and transport may recommend an appropriate transport medium when transport is delayed, to enhance recovery of bacterial pathogens, such as placing the specimen in a vial with Cary-Blair transport medium.
WOUND	Wounds must only be cultured when infection is strongly suspected, to avoid misinterpreting colonization. Superficial wound samples using swabs should be avoided, unless the wound is opened at the time by the health care provider and pus is present, or aspiration of underlying fluid collection is performed. If needed, wash the wound with saline and take the sample pressing borders. Use proper transport media like Amies or Stuart. For transporting tissue collected in surgery rooms, use a sterile container with sterile saline moistened gauze.

<p>BODY FLUIDS</p>	<p>Body fluids should be collected only by an experienced individual, in appropriate conditions. The CML should provide the materials required to collect and transport body fluids. Sterile tubes without additives are preferred for culture purposes. For aerobic and anaerobic cultures submit 10 ml of fluid, and for viral isolation, send 3 ml or less in a sterile vial (1 ml minimum). If tuberculosis or fungal infections are suspected, collect a minimum of 5 ml of fluid into a sterile container. Transport immediately. Do not send sterile body fluids on swabs.</p>
<p>RESPIRATORY SAMPLES</p>	<p>For sputum samples, rinse mouth with tap water; patient should then breathe deeply, and cough repeatedly to achieve a deep specimen and expectorate. Sample must be collected into dry sterile containers. Transport immediately at ambient temperature. Refrigerate if a delay of over 1 hour is anticipated. Expecterated sputum is acceptable for bacterial, mycobacterial, and fungal cultures, but not for viral cultures. Microbiology will determine the number of squamous epithelial cells present for specimen adequacy and reject samples for bacterial culture that are not indicative of deeply expecterated specimens. Bronchial brush, wash, and lavages should be performed by experienced individuals. Samples should be transported in sterile containers immediately, at ambient temperature.</p>

Adapted from *Diagnostic stewardship. A guide to implementation in antimicrobial resistance surveillance sites*. World Health Organization, Geneva, 2016. Available at:

<http://www.who.int/glass/resources/publications/diagnostic-stewardship-guide/en/>

Table 4 provides a description of all essential and achievable activities and future goals for the clinical microbiologist in an antimicrobial stewardship program.

TABLE 4. ESSENTIAL AND ACHIEVABLE ACTIVITIES, AND FUTURE GOALS OF THE CLINICAL MICROBIOLOGY LABORATORY	
STEWARDSHIP LEVEL	DESCRIPTION
1. ESSENTIAL	<p>Provide timely, reliable and reproducible identification of microbes (viruses, bacteria, yeast, parasites, etc.), and clinically relevant antimicrobial susceptibility reports. Discuss updates of antimicrobial susceptibility methods and prescription alerts with infectious diseases clinicians.</p> <p>Actively participate in the AST to discuss issues related to clinical microbiology lab performance, and its impact on prescribing decisions and antimicrobial resistance in the hospital.</p> <p>Promptly report new or critical patterns of resistance (e.g., new mechanisms, new species); provide supplementary results for drugs that may be a therapeutic alternative; and report to the infection prevention and control team to prevent outbreaks.</p> <p>Provide, review and publish cumulative antimicrobial susceptibility reports using international standards – like CLSI*- depending on hospital size and number of cultures. If indicated, breakdown reports by hospital unit.</p> <p>Participate in proficiency testing programs to guarantee reliability of results.</p> <p>Provide guidance on correct sample collection and transportation to the clinical microbiology laboratory. Develop workshops on the subject for nurses and other clinicians.</p>
2. ACHIEVABLE	<p>In collaboration with the AST, the CML may provide comments to guide therapy on specific mechanisms of resistance.</p> <p>Participate in establishing protocols on biomarker use.</p> <p>Use rapid diagnostic platforms for critical specimen types (respiratory tract, central nervous system, etc.), and develop guidelines for interpreting results.</p> <p>Incorporate and guide the correct use of diagnostic techniques for <i>Clostridium difficile</i> infections.</p> <p>Participate in ASP education programs for prescribers and patients.</p>
3. FUTURE GOALS	<p>Evaluate feasibility of antimicrobial susceptibility testing for new drugs.</p> <p>Expand the use of rapid microbiology tests for molecular detection of pathogens (e.g., multiplex PCR, QuickFISH®).</p> <p>Participate in national and regional surveillance systems.</p>

*CLINICAL LABORATORY STANDARDS INSTITUTE.

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... Many successful prescription-based strategies can be implemented in hospital ASPs. However, no single template fits all hospitals. In fact, one key feature of successful ASPs is their potential to adapt to the specific characteristics and circumstances of every hospital setting ...



Based on the table above, the clinical microbiology laboratory can contribute to the success of ASPs in several ways. Following is a more detailed explanation of two of the main activities that have clinical impact:

Testing and reporting antimicrobial susceptibility: To provide clinically relevant results, it is important to test and to interpret the right drugs. Some recommendations include:

- » Choose the best methods for your institution, considering the need to provide minimum inhibitory concentrations (MICs), turnaround time, accuracy, adaptability, capacity.
- » Follow international standards to choose drugs for testing and reporting. Standardized breakpoints and interpretative criteria are crucial to obtaining homogeneous results, and to make them comparable throughout centers and countries. Following previous PAHO recommendations, CLSI standards are suggested.
- » Do not report drugs that do not concentrate at the site of infection, such as fluoroquinolones in central nervous system infections, despite susceptible test results.
- » For microorganisms with intrinsic resistance mechanisms to certain drugs, such as *Pseudomonas aeruginosa* to ertapenem, the drug should be reported as resistant regardless of laboratory test results.
- » Read and interpret results with caution. Watch for possible resistance mechanisms, perform confirmatory tests, and use CLSI reporting criteria.
- » Include internal quality control strains for accurate results. The American Type Culture Collection or ATCC provides strains with specific resistance mechanisms to control detection methods and MICs.
- » Subscribe to a proficiency testing program with an accredited institution. To choose the best program, consider methods, feedback, advice, etc.

Based on local policies and guidance provided by the AST, the CML could develop guidelines for cascade reports with hidden/restricted antimicrobials to prevent the use of wrong agents (i.e., unnecessary broad spectrum) (45), as suggested in Annex I.

Rapid diagnostic tests: The CML is amid a diagnostic revolution. New molecular diagnostic technologies have the potential to transform the modern CML and the care of patients with suspected infections by providing more rapid and robust microbiological diagnoses (46,47). Some current methods available are summarized in Annex I.

Following is a description of clinical microbiology laboratory activities, by level of development of the ASP.

A. LABORATORY ACTIVITIES IN BASIC ANTIMICROBIAL STEWARDSHIP PROGRAMS

- » *Correct sampling*: Develop sampling and transportation guidelines for your institution. Provide details regarding times, collection techniques and proper transportation media for optimal microbe recovery. It is important to include rejection and acceptance criteria, as well as instructions for forwarding to reference laboratories.
- » *Specimen handling and culture*: Develop a diagnostic microbiology handbook to standardize laboratory methods, from basic stains, like Gram or Ziehl-Neelsen, to culture interpretation, to avoid reporting contaminants or microbes with non-relevant thresholds.
- » *Prompt report of basic tests*: Rapid turnaround times for stains, like Gram or Ziehl-Neelsen, can support prompt decisions related to starting or suspending the administration of antimicrobials. The laboratory should have a list of results deemed urgent, such as positive blood cultures, body fluids, and biopsy specimens.
- » *Identification of microorganisms*: The laboratory should be able to identify common bacteria and yeasts to the species level. If not feasible, the lab should at least be able to perform basic tests, such as chromogenic media, to separate *Candida albicans* from other species. If the latter is not possible, strains should be properly referred to a central clinical microbiology laboratory.

B. LABORATORY ACTIVITIES IN INTERMEDIATE ANTIMICROBIAL STEWARDSHIP PROGRAMS

- » Perform antimicrobial susceptibility testing for fastidious organisms and yeasts, when clinically relevant, and following international standards, such as the CLSI's. Fungal and anaerobe antimicrobial susceptibility testing should also be performed when necessary. The identification of resistance mechanisms is important, such as carbapenemases in gram-negative rods.
- » *Viral testing*: The microbiology laboratory could implement specific tests to detect viruses in respiratory or body fluid samples.

C. LABORATORY ACTIVITIES IN ADVANCED ANTIMICROBIAL STEWARDSHIP PROGRAMS

- » Apply molecular diagnostics to patient care: MALDI-TOF and syndromic testing are cutting edge technologies in diagnostic microbiology. Depending on local epidemiology and case complexity, consider implementing diagnostic panels for the most common syndromes in your institution. Develop guidelines to request testing and interpret results. Prompt turnaround, together with AMS, is the key to cost effectiveness.
- » Broaden diagnostics for viral infections: Perform tests to detect the most common viruses in body fluids, blood, tissues, etc.
- » Molecular diagnosis of antimicrobial resistance: Implement rapid methods for detection of the most common antimicrobial resistance markers. Include the information retrieved into a database to generate statistics for surveillance decisions, and to adjust local antimicrobial guidelines.

11.5. Information Technology in Antimicrobial Stewardship Programs

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A successful ASP needs adequate indicators. The use of proper and up-to-date information is essential. The availability of electronic prescriptions and electronic medical records is useful for many information technology initiatives. Countries should, therefore, start consolidating and implementing these types of systems.

USES OF INFORMATION TECHNOLOGY IN ANTIMICROBIAL STEWARDSHIP PROGRAMS

a. Measuring antimicrobial consumption

There are several metrics for the consumption and use of antimicrobials (48). For example, daily defined doses or DDDs/1000 patient-days may be easier to obtain than days on therapy (DOT) (https://www.whocc.no/atc_ddd_index/), although the latter could be more accurate when measuring consumption. Whatever metric is chosen based on hospital characteristics (human and material resources), information technology is essential to capture data needed for calculations. These indicators must, nonetheless, be adapted to each facility's conditions.

b. Clinical outcomes

These include infection complications, antimicrobial use, length of stay, mortality and readmissions, which may also be collected, analyzed and reported by means of information technology (49).

c. Access to microbiological data

IT staff are critical if one is to integrate stewardship protocols into existing information workflows. This information should register data from specific patients, as well as provide access to epidemiological data by unit, hospital or region. Microbiology records should be easily accessible at the point of care (ward, unit). Also, a computerized system would help the laboratory communicate findings of epidemiologically important organisms or resistance mechanisms (MRSA, vancomycin-resistant enterococci [VRE], carbapenemase producing Enterobacteriaceae, multidrug resistant *Pseudomonas aeruginosa* and *Acinetobacter* spp). Software to detect epidemiological changes should be available.

Software, such as WHONET (50), linked to the hospital's central information network should be available at the point of care. Recently, this information proved valuable in detecting MRSA infections in the community in Latin America (51) and the dissemination of high-risk clones of extensively drugs resistant *Pseudomonas aeruginosa* in Colombia (52).

d. Pre-prescription authorization

This strategy, previously described in section 11.3, is frequently used in ASPs, and it can be manually executed and/or with computer assistance.

e. Specific antimicrobial use

Where preauthorization is not required, a simple way for the antimicrobial stewardship team to audit the use of specific drugs (section 11.3, above) is to daily review electronic lists of antimicrobials deserving special attention, such as carbapenems, and antifungals.

f. Automatic stop orders

These systems are very useful to prevent prolonged antimicrobial prophylaxis after surgery (see section 11.3, above.)

g. Clinical decision support systems

Clinical decision support systems (CDSS) range from mobile applications to approval systems, electronic medical records, computerized physician order entry, and advanced decision support (41,53). Today, the widespread use of smartphones and the relative simplicity of producing apps in the field of antimicrobial stewardship are valuable technologies to consider in Latin America and the Caribbean. Many CDSS have proven advantageous, for instance, to facilitate drug approvals; to improve communications in real-time among prescribers and the AST; to reduce the administration of redundant antimicrobial therapy (two or more drugs with similar spectra), and overall antimicrobial use, costs and length of stay (54).

Some CDSS link patient information, such as medical records, and complementary studies, to optimize antimicrobial therapy, including data on drug interactions and dose adjustments in cases of renal or liver diseases. Among the main disadvantages of CDSS and surveillance systems are the time and financial resources required for their implementation and maintenance.

Computer support within an ASP can be progressively adopted. Minimum requirements are databases of antimicrobial consumption by unit (see section 11.6). As the program advances, the need for systems gathering patient data and some CDSS could be increasingly implemented. Table 5 summarizes information technology interventions by degree of development of the ASP.

TABLE 5. INFORMATION TECHNOLOGY INTERVENTIONS, BY LEVEL OF DEVELOPMENT OF THE ANTIMICROBIAL STEWARDSHIP PROGRAM

BASIC LEVEL	INTERMEDIATE LEVEL	ADVANCED LEVEL
DATABASE OF ANTIMICROBIAL CONSUMPTION, BY HOSPITAL UNIT; DATABASE OF BACTERIOLOGIC SURVEILLANCE, BY HOSPITAL UNIT	Electronic prescriptions and charts	Calculations of antimicrobial consumption (e.g., defined daily doses or DDDs/1000 inpatients/day)
	Alerts of specific antimicrobial use	Estimates of clinical outcomes related to antimicrobial treatment
	Time-sensitive automated stop orders for surgical prophylaxis	National, regional or hospital's applications with guidelines
	Electronic guidelines (by electronic mailings to prescribers, intranet)	Point of care access to microbiologic results from all units
		Clinical decision support systems (commercial or homegrown) of different levels of complexity

11.6 Monitoring and Evaluation of Antimicrobial Stewardship Programs

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ASPs should be monitored and evaluated. The impact of ASPs can be assessed by process or outcome indicators in every setting. One peer-reviewed study of the impact of ASPs focusing on patient outcomes indicates that the choice of metrics is influenced by data availability and resources (55). The review provides a starting point for compiling standard outcome metrics for assessing ASP. Bumpass et al. (56) surveyed infectious diseases physicians and pharmacists regarding antimicrobial stewardship metrics considered important in ASP assessment. The authors reported that appropriateness of antimicrobial use, infection-related mortality, and antibiotic associated length of stay were considered the most important outcomes, but antimicrobial use and costs were the most commonly collected metrics.

1. OUTCOME INDICATORS

Outcome measures may be categorized as microbiological, patient-related or financial.

A. MICROBIOLOGICAL OUTCOMES

Indicators of microbiological outcomes include percentage of difficult to treat organisms, such as MRSA, ESBL-producing Enterobacteriaceae, rate of isolation of resistant organisms, and rate of *Clostridium difficile* infections (57). Assessing the impact of ASPs on resistance using said indicators has inherent limitations. This can be explained by several factors that affect the development of resistance, which makes it difficult to establish a clear causal association between AMS interventions and decrease in resistance. However, ASPs – especially those restricting the use of high-risk antibiotic classes (like third-generation cephalosporins and fluoroquinolones) – have been shown to reduce resistance and/or improve bacterial susceptibility.

The rate of *Clostridium difficile* infections (CDI) has been used to assess ASP effectiveness. Programs restricting or avoiding high-risk antibiotic classes and clindamycin have been associated with significant decreases in *Clostridium difficile* infection rates. However, such decreases occurred in the presence of strong infection prevention and control measures, which make the association between ASP and the reduction in CDI rate difficult to determine. Nonetheless, IPC alone has shown not to be effective in controlling outbreaks of CDI. A significant reduction in rates of both CDI and ESBL producers followed stewardship interventions that involved restriction or avoidance of high-risk antibiotics, as ciprofloxacin and ceftriaxone (58, 59, 60).

B. CLINICAL OUTCOMES

ASP impact indicators include all-cause hospital mortality, length of stay, and readmission rates. Clinical improvement and rate of adverse antimicrobial reactions have also been recommended indicators of clinical outcomes (10). It is difficult to establish a clear causal association between ASP interventions and indicators such as hospital mortality and length of stay, due to confounders (61). Mortality related to antimicrobial resistant organisms and infection-related hospital stay have been suggested as better impact indicators. Okumura et al. (62) reported lower 30-day mortality with bundled ASP measures secondary to an intervention consisting of clinical pharmacist chart review; discussions between microbiologists and infectious diseases physicians; local education; and continued follow-up, when compared to conventional ASP activities.



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“We must recognize that acting as an antimicrobial steward will often involve making important value judgments.”

Littmann J, Viens AM

C. FINANCIAL OUTCOMES

Stewardship programs can significantly reduce annual drug costs; these savings will be even higher if costs other than drug-related are also calculated (63), and have been helpful in garnering support for ASPs. If hospitals monitor antibiotic costs, consideration should be given to assessing the pace at which those costs increased before the start of the ASP. After an initial period of marked cost savings, antibiotic use patterns and savings often stabilize, so permanent decreases in antibiotic use and costs should not be expected. However, it is important to continue supporting the ASP to sustain gains, as costs can increase if programs are terminated. Many programs that assessed the impact of ASPs on antimicrobial use also assessed cost savings. Table 6 shows examples of antibiotic use reduction and cost savings when implementing an ASP. Irrespective of variable monetary savings, clinical and microbiological outcomes by themselves justify the development and support of long-lasting ASPs in every hospital setting.

TABLE 6. IMPACT OF ANTIMICROBIAL STEWARDSHIP PROGRAMS ON ANTIMICROBIAL USE AND COST

STUDY/REFERENCE	HOSPITAL SIZE AND TYPE	INTERVENTION	STUDY TYPE	MEASURED IMPACT
VETTESE ¹	253-bed community hospital	IV to oral conversion, dose optimization, review	Before-after	6.4% decline in days of therapy and 27% reduction in total antimicrobial expenditure
CISNEROS ²	1251-bed teaching hospital	Education and training, guidelines, counseling, interviews, feedback	Before-after	Reduction in antimicrobial consumption from 1150 DDD/1000 patient days to 852 DDD/1000 patient days, with 42% reduction in antimicrobial expenditures
BORDE ³	1600-bed teaching hospital	Guidelines revision information and education, review and feedback	Before-after with interrupted time series	Significant decline in overall antibiotic use ($p < 0.001$)
BARTLETT ⁴	155-bed community hospital	Formulary restriction, IV to oral conversion, automatic stop, review and feedback	Before-after	Acquisition costs decreased from \$569,786 to \$424,433 with a direct cost savings of 25.5%. Antimicrobial use decreased from 1627 to 1338 DDD/100 patient-days (17.8%).

¹Vettese N, et al. Outcomes associated with a thrice-weekly antimicrobial stewardship program in a 253-bed community hospital. *J Clin Pharm Ther* 2013;38:401-404.

²Cisneros J, et al. Global impact of an educational antimicrobial stewardship program on prescribing practice in a tertiary hospital centre. *Clin Microbiol Infect* 2014;20:82-88.

³Borde J, et al. Feasibility and impact of an intensified antibiotic stewardship program targeting cephalosporin and fluoroquinolone use in a tertiary care university medical center. *BMC Infect Dis* 2014;14:201.

⁴Bartlett J, et al. Implementation and first-year results of an antimicrobial stewardship program at a community hospital. *Am J Health-Syst Pharm* 2014;71:943-949.

2. ANTIMICROBIAL STEWARDSHIP PROGRAMS MONITORING INDICATORS

The AST, together with hospital authorities, should choose the best metrics and indicators for their institution's characteristics and capacities, and the degree of program development. Table 7 summarizes several different variables or measures for monitoring an ASP.

TABLE 7. ANTIMICROBIAL STEWARDSHIP PROGRAM MONITORING INDICATORS		
VARIABLE	INDICATOR	INDICATOR CONSTRUCTION
ANTIMICROBIAL CONSUMPTION	Defined daily dose (DDD) (*)	$\text{DDD per 1000 patient days} = \frac{\text{grams consumed of an antimicrobial in a given period} \times 1000}{\text{DDD} \times \text{total number of patient days within the period}}$
	Days of therapy (DOT)	$\text{DOT per 1000 patient days} = \frac{\text{days of therapy with an antimicrobial in a given period} \times 1000}{\text{Total number of patient days within the period}}$
COST OF ANTIMICROBIALS	Costs of antimicrobials per patient-day	$\frac{\text{Total cost of consumed antimicrobial agents in a given period} \times 1000}{\text{Total number of patient days within the period}}$
	Costs per DDD consumed	$\frac{\text{Total cost of consumed antimicrobial agents in a given period}}{\text{DDDs consumed within that period}}$
APPROPRIATENESS OF ANTIMICROBIAL USE	Inappropriate DDDs	$\frac{\text{Inappropriate DDDs}}{\text{DDDs consumed}}$
	Adherence to clinical guidelines	$\frac{\text{Indications for a disease based on clinical guidelines} \times 100}{\text{total number of indications for that disease}}$
	De-escalation	$\frac{\text{Number of de-escalations from empiric therapy} \times 100}{\text{Total number of indicated empiric treatments}}$
	Switch to oral route	$\frac{\text{Number of effectively switched regimens to oral route} \times 100}{\text{Total number of regimens that can be switched to oral route}}$
	Length of therapy	$\frac{\text{Total days of treatment for a specific disease}}{\text{total number of cases treated}}$
	Surgical prophylaxis within 60 minutes prior to procedure	$\frac{\text{Surgical prophylaxis administered within the 60 minutes prior to surgery} \times 100}{\text{Total number of surgeries requiring prophylaxis}}$
	Surgical prophylaxis stopped within 24 hours after surgery	$\frac{\text{Surgical prophylaxis stopped within 24 hours after surgery} \times 100}{\text{Total number of surgeries requiring prophylaxis}}$

OUTCOME	In-hospital mortality	Number of deaths by type of infection / Total number of patients with that infection
	Mean time of hospitalization	Days of hospitalization by type of infection / Total number of patients with that infection
	Readmission at 30 days	Patients with infections who are readmitted within 30 days after discharge / Total number of patients with that specific infection who were discharged alive
	Multidrug-resistant infection (MDR)	Number of non-duplicated infections by type of MDR in a period x 1000 / Total number of patient days within that period
	<i>Clostridium difficile</i> infection	Number of hospital-acquired <i>C. difficile</i> infections in a given period x 1000 / Total number of patient days within that period

(*) DDD per 1,000 patient days is the most commonly used quantity measure of antibiotic use because of the availability of the required data needed for its calculation in many settings. For detailed guidance on how to calculate the DDDs, refer to http://www.who.int/medicines/regulation/medicines-safety/toolkit_indicators/en/index1.html

Patient outcome must be a key component of the ASP evaluation. The choice of indicator is influenced by data availability and resources, as well as each hospital's need to show a specific impact. ASPs should start with simple indicators, and increase their complexity as ASTs are consolidated, and the hospital data-base becomes easier to access. When designing a study, consideration must be given to confounders and unintended adverse consequences and their control, to adequately capture the impact of an ASP.

11.7 Ethical and Legal Considerations, and Economic Issues

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“We must recognize that acting as an antimicrobial steward will often involve making important value judgments” (64).

As discussed throughout these recommendations, an ASP requires constant decision-making regarding prescription control and access to certain antimicrobials; de-escalation; treatment suspension if the need for an antimicrobial is not solidly supported; automatic stop orders; and other strategies that impose ethical and, eventually, legal considerations.

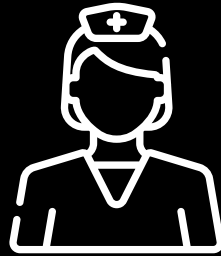
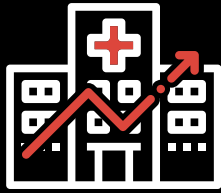
Given the direct consequences of AMR, restricting antibiotic use to instances in which they prevent a substantial risk of irretrievable harm to individuals might be ethically justifiable (65). Physicians, therefore, may have to expose patients to higher risks of complications, longer

duration of illness, or increased mortality risk, if the expected benefit of immediate antibiotic therapy is not considered substantial enough. This dilemma between the need for responsible and restrictive use of antimicrobials on one hand, and physicians' obligations to their patients on the other is an ethical challenge that requires urgent attention from policy-makers. A call for effective and expansive antimicrobial stewardship will inevitably imply restrictions beyond the mere avoidance of waste. However, if physicians are not provided with clear guidelines on when antibiotic use can be rightfully withheld, they face a severe ethical dilemma in their everyday practice (66). On the other hand, guidelines by themselves are unlikely to solve all ethical concerns related to the rational use of antimicrobials.

Judicious use of antimicrobials is a key element of stewardship, but making antimicrobials available in low or middle-income settings is also essential (See section I.4). Making diagnostic tools and resources accessible where they are most needed is an imperative. *There is no sense for antimicrobial stewardship where antimicrobials are not available...* And this also poses a moral and ethical dilemma.

Prescribing antimicrobials is a decision of the attending professional; it is also a personal act with individual responsibility. Most antimicrobials –both in outpatient health care services and hospitals– are prescribed by primary care physicians, many without specific training in microbiology or infectious diseases (67). Health authorities, whether at the national, regional or hospital level, should be responsible for defining appropriate prescription auditing and supervision mechanisms (see also section I.3). Determining who should be accountable is crucial. Undoubtedly, the primary care physician assumes most of the responsibility of antimicrobial prescriptions, but, when the AST is involved in the decision process, that responsibility is shared. In an international survey of 74 countries (68), the main responsibility fell to the treating physician, shared with the adviser, a member of the AST. This shared responsibility was greater when there was direct examination of the patient and written advice. Inappropriate use of antimicrobials could eventually be considered malpractice. However, by providing knowledge through education and practice guidelines, firm support to stop indications, and prompt approval of orders are steps in the right direction.

Because ASPs usually save money, they should have financial support at the national (MOH) and local levels (each participating institution). Undoubtedly, these programs are cost-effective, but their implementation requires funds for key players. Dedication to the program needs to be recognized. In fact, just a couple of interventions (implementation of only one preoperative dose for surgical prophylaxis, and review and feedback of carbapenems) might save sufficient funds to sustain an ASP.



Part III

Antimicrobial Stewardship in
Primary Health Care (PHC)

III.1. Organizational Aspects

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A. RELEVANCE OF ANTIMICROBIAL STEWARDSHIP PROMOTION IN THE COMMUNITY

Global antibiotic consumption increased by 65% between 2000 and 2015, from 21.1 to 34.8 billion DDDs, while antibiotic consumption rate increased 39% from 11.3 to 15.7 DDDs per 1,000 inhabitants per day over the study period (69). This increase in global consumption was primarily driven by increased consumption in low- and middle-income countries, where consumption increased 114%, from 11.4 to 24.5 billion DDDs, and the antibiotic consumption rate increased 77%, from 7.6 to 13.5 DDDs per 1,000 inhabitants per day. It is estimated that the proportion of antimicrobials in outpatient settings varies a great deal by country – from as low as 40% in Thailand to 95% in Poland and New Zealand (R Laxminarayan, personal communication).

Around 60% of all antimicrobial consumption in human health in the United States of America occurs in outpatient health services (70), including antimicrobial prescription in public and private primary health care (PHC) services by medical specialists and other health professionals. In many Latin American and Caribbean countries, enforcement of antimicrobial prescription and sales regulations is weak, and in some countries, antimicrobials are often purchased without prescription (over the counter or off-exchange trade) (8). Estimates indicate that half of all community antibiotic use is inappropriate, administered to treat self-limited infections, such as colds, coughs and acute diarrhea, which not only does not benefit patients, but adds to the increasing burden of antibiotic resistance (9). Furthermore, antibiotics are among the most common causes of adverse drug events in children and adults (1).

Despite the high volume of antimicrobial consumption in ambulatory care in low- and middle-income countries, antimicrobial resistance is underreported, and the development of interventions targeting antimicrobial use is still scarce (71). These are not easy tasks. Unlike hospital settings, where problems and target audiences for interventions are contained and often traceable, addressing antimicrobial use in the community poses great challenges: identifying determinants of antimicrobial misuse (knowledge, expectations, cultural predilections and beliefs) is complex, as is the identification of all actors involved (prescribers, dispensers and community members). All these determinants and individuals influence the patterns of antimicrobial use in the community, and are examples of micro-level determinants of antimicrobial use. Other systemic factors, such as health care system characteristics, pharmaceutical markets and regulatory environment, are also important determinants of antimicrobial use at the community level (72, 73) (Figure 2).

Antimicrobial stewardship initiatives targeting community level use of antimicrobials must address the above determinants, and must aim at modifying the knowledge, attitudes and behaviors of diverse stakeholders, and to change the context in which the latter interact (6,75). It is, therefore, important to keep in mind that promoting judicious use of antimicrobials must be aligned with existing policies and/or guidelines on improving the utilization of all medicines.

Countries should develop comprehensive national action plans on antimicrobial use, that cover a wide array of educational, managerial, economic and regulatory interventions, coordinated by high level national authorities (26, 74, 75, 76). Following is a list of recommended strategies to promote the rational use of antimicrobials, by scope level.

Macro-level: advocacy and regulatory interventions

- » Establish a multidisciplinary national body to coordinate policies on antimicrobial use and antimicrobial resistance; provide resources and political support.
- » Draft and disseminate a national program: prioritize problems, define objectives, assign responsibilities, and develop indicators to monitor and evaluate interventions.
- » Ensure and enforce appropriate regulation of:
 - *medicines licensing (e.g., only allow registration of antimicrobials that meet international standards; avoid inappropriate combinations);*
 - *enforce prescription-only status for antimicrobial sales;*
 - *licensing requirements for prescribers and dispensers;*
 - *promotion and advertising of medicines;*
 - *financial incentives that encourage inappropriate use (e.g., not allowing linkage between prescribing and selling practices);*
 - *antimicrobial stewardship criteria for accreditation of health services;*

Meso-level: managerial interventions

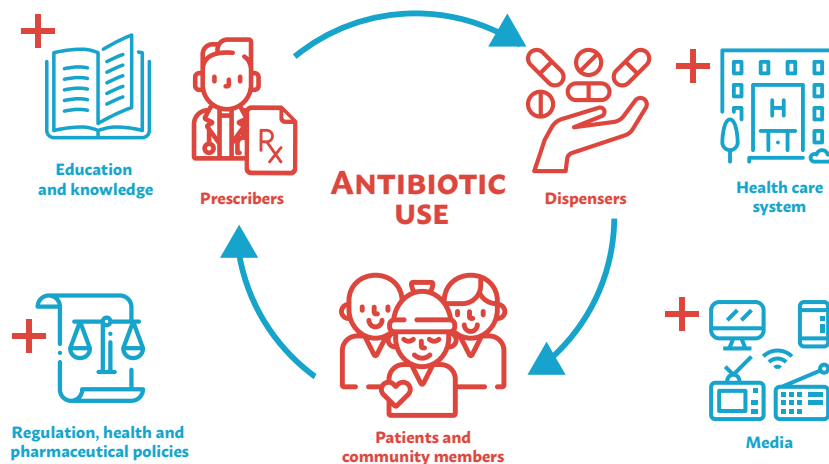
- » Develop standard treatment guidelines for common infectious diseases, such as community acquired pneumonia, otitis media, skin and soft tissue infections, sinusitis, complicated urinary tract infections. Guidelines should be based on essential medicines lists, and based on local patterns of antimicrobial resistance in those communities.
- » Develop and implement strategies to encourage the use of standard treatment guidelines for drug procurement and prescription.

- » Establish district-level antimicrobial stewardship committees for primary health care and hospitals, to monitor and promote optimization of antimicrobial use at the local level. Dedicated staff and incentives for committee members should be provided.
- » Establish a system for routine supervision, audit, and feedback of prescribing practices in primary health care and hospitals.
- » Establish microbiology partnerships within local hospitals to monitor the evolution of antimicrobial resistance in common outpatient infections, and share the data with local prescribers.

Micro-level: educational interventions

- » Improve undergraduate and maintain in-service education for health care professionals based on standard treatment guidelines, essential medicines lists, and local antimicrobial susceptibility patterns.
- » Develop and disseminate evidence-based information on antimicrobials and their proper use among health care providers and patients (printed or electronic bulletins, formularies).
- » Develop public education campaigns on judicious antimicrobial use.

Figure 2. Determinants of Antimicrobial Use in the Community



B. ORGANIZING ANTIMICROBIAL STEWARDSHIP PROGRAMS IN PRIMARY HEALTH CARE

Successful implementation of ASPs in primary health care requires adapting health systems, mainly, to promote the optimization of antimicrobial use. For that purpose, there needs to be interaction among various national institutions and organizational levels, as well as with private and non-governmental organizations (e.g., professional associations, pharmacies' organizations), to ensure a cohesive approach to antimicrobial resistance (9, 77). The main steps in organizing ASPs for ambulatory care services are described below.

a) Governance. Effective governance is essential to the successful implementation and sustainability of any ASP. This requires the designation of a specialized office (national ASP) within the Ministry of Health. Such office must have executive authority and resources to coordinate efforts among relevant stakeholders, and must be directly supported by and accountable to its assigned secretariat in the MOH. Placing the national ASP within a department of the MOH with experience in health care delivery and quality of care provides added value in achieving shared objectives (77). The development and implementation of ASPs is one of the five main objectives of the 2015 WHO AMR Global Action Plan (objective number 4) (26). Said action plan provides guidance on the governance structure. However, because of the number and diversity of stakeholders, and given the activities required for ASP development and implementation at the community level, the WHO framework needs to be tailored to each country's needs.

The MOH's national ASP should have the following responsibilities:

- » To review and analyze the status of national ASPs, including stakeholder participation.
- » To establish an executive committee with relevant stakeholders.
- » To draft and disseminate the national ASP's guide, including an executive statement.
- » To develop a monitoring and evaluation plan.
- » To oversee the implementation of local ASPs at all subnational levels (states, provinces, districts).

Ideally, focal points for implementing and monitoring antimicrobial stewardship activities should be designated at different subnational levels.

b) Stakeholder participation. Given the complex nature of antimicrobial use in the community, early involvement (i.e., prior to drafting the antimicrobial stewardship plan) of relevant stakeholders is key to ensure the adequacy and feasibility of interventions, as well as to obtain political commitment and guarantee the program's sustainability. When designing interventions, consideration must be given to socioeconomic and other country specific conditions, based on local situation analyses (78). For example, initiatives involving the pharmaceutical industry are politically charged, mainly, because they affect political/economic interests, such as physicians' associations, and pharmaceuticals industry lobbying groups. Building alliances among supporters and reaching consensus with opponents is necessary during the design phase of the ASP, as well as for the development and implementation of the guidance document (76, 79). Different potential stakeholders and their roles are exemplified below. Practical guidelines for identifying and bringing together stakeholders have been published elsewhere (80).

Potential Stakeholders in a National Antimicrobial Stewardship Program Committee and Functions

Ministry of Health Departments

- » *Quality of care:* ASP coordination, development and implementation of standard treatment guidelines, prescription audits (public and private health sectors), medical education, monitoring and evaluation of interventions for health providers.
- » *Health promotion:* Design, implementation and evaluation of public campaigns.
- » *Regulatory agency:* Development and enforcement of regulations related to antimicrobial licensing, advertising and dispensing.
- » *Epidemiological surveillance:* Providing feedback on antimicrobial susceptibility for the development of standard treatment guidelines and essential drugs lists. Coordination among national reference laboratory, academic institutions, public and private laboratories to strengthen AMR surveillance.
- » *Program managers:* Including ASP activities and indicators in relevant programs (HIV/AIDS/STI, TB, integrated management of childhood diseases, acute respiratory infections and diarrheal diseases).

Public and Private Health Institutions

- » Establishment of ASP committees, systems for routine supervision, audit, and feedback of prescribing practices;

in-service education for health professionals based on standard treatment guidelines and local susceptibility patterns; and development and implementation of campaigns on antimicrobial resistance and stewardship (e.g., during the World Antibiotic Awareness Week).

Public and Private Accreditation Groups

- » Include ASP activities in patient safety and care standards for hospitals and primary health care.

Researchers and Academia

- » Providing evidence to support AMR surveillance and understand antimicrobial use; the development of campaigns and educational interventions and materials for prescribers and the public.

Professional Associations (medical, microbiology, pharmacy, nursing)

- » Including antimicrobial resistance and stewardship concepts in continuing medical education, and for professional accreditation. Participation in World Antibiotic Awareness Week activities.

Pharmacies: Retail Associations

- » Including antimicrobial resistance and stewardship concepts in educational activities for pharmacy staff. Participation in the World Antibiotic Awareness Week.

Medical, Pharmacy, Dentistry and Nursing Schools

- » Including antimicrobial resistance and stewardship concepts in undergraduate curricula. Joint campaigns during the World Antibiotic Awareness Week.

Patient and Consumer Associations

- » Organizing educational activities on antimicrobial resistance and responsible use of antimicrobials. Participation in the World Antibiotic Awareness Week.

Media (health reporters, radio, television and print)

- » Organizing educational activities on antimicrobial resistance and the responsible use of antimicrobials, and reporting on said topics. Participation in the World Antibiotic Awareness Week.

Within the ASP committee, subcommittees could assume responsibility for each component of the program (or sub-programs), for which experts on each field may be convened:

- » Regulation of antimicrobials commercialization (sales, advertising)
- » Medical education (pre- and in-service)
- » Prescription quality in ambulatory care
- » Licensing requirements
- » Prescription audit
- » AMR monitoring, surveillance and information management and dissemination
- » Public awareness

c. Situation analyses and ASP guidance drafting. Right after the national ASP committee has been established, it should document the extent of antimicrobial use at the community level, and its context (80). Limited information on these topics provides an opportunity to encourage further research. Practical guidance on data collection and rapid assessments (or baseline situation analysis) has been published by Management Sciences for Health (80). The situation analysis could address the following: a) current regulations of antimicrobials sales and their enforcement; b) assessments of antimicrobial consumption levels and prescription appropriateness (private and public health care sectors); c) knowledge, attitudes and practices related to antimicrobial use among various stakeholders (e.g., general practitioners, medical specialists, pharmacy personnel, patients and their families); and d) identification of economic incentives that encourage inappropriate use or optimal practices related to antimicrobials.

Situation analyses should be followed by defining and prioritizing the most significant problems of antimicrobial use in PHC, their underlying causes, and the most effective and feasible interventions to address them (Box 3). Situation and priority analyses can be useful in defining ASP core objectives, and the main strategies and activities to accomplish them. Output and outcome indicators can also be developed at this stage. To facilitate monitoring and evaluation of the ASP, a logical framework approach is recommended (81). Ensuring proper dissemination of the ASP document (for example, by involving the media and public figures or 'champions') is important for the program's success and sustainability.

**BOX 3. ANTIMICROBIAL USE IN PRIMARY HEALTH CARE SETTINGS:
A SAMPLE OF PROBLEMS TO BE ADDRESSED BY THE PROGRAM**



» **Self-medication with antimicrobials, lack of enforcement of prescription-only status for antimicrobial sales**



» **Inappropriate prescription (non-adherence to standard treatment guidelines)**

- ✗ Unnecessary prescription of antibiotics (e.g., acute bronchitis, nonspecific upper respiratory infection, viral pharyngitis, self-limited acute diarrhea).
- ✗ Empiric prescription instead of test-based diagnosis (e.g., diagnosing streptococcal pharyngitis and prescribing antibiotics without testing for group A Streptococcus).
- ✗ Wrong agent, dose, or duration of therapy (e.g., azithromycin rather than amoxicillin or amoxicillin/clavulanate for acute bacterial sinusitis; more than three days of antibiotic treatment for uncomplicated urinary tract infections in otherwise healthy women; redundant treatment with two or more antibiotics).
- ✗ Suboptimal or delayed prescription for conditions requiring antibiotic treatment (e.g., community-acquired pneumonia, urinary tract infection, skin and soft tissue infections).
- ✗ Early prescription of antibiotics when watchful waiting or delayed prescribing might be appropriate instead (e.g., acute otitis media with mild symptoms or acute uncomplicated sinusitis).



Source: Adapted from Sanchez GV, Fleming-Dutra KE, Roberts RM, Hicks LA. Core elements of outpatient antibiotic stewardship. *MMWR Recomm Rep* 2016;65 (No. RR-6):1-12. Available at: https://www.cdc.gov/antibiotic-use/community/pdfs/16_268900-A_CoreElementsOutpatient_508.pdf.

d) *Implementation and scaling-up.* National-level progress on AMR takes time. It takes several years to generate evidence and awareness of the problem, and to establish effective governance to fully implement national interventions (9). In the meantime, the AST should begin step-by-step and proper implementation of program interventions, gradually increasing the number of components, as well as territorial coverage. This stage-wise approach to AMS implementation could

improve antibiotic use, and validate ASP team members, while progress is achieved. The staged implementation also provides learning lessons for full-scale implementation (9).

Similarly, implementation of antimicrobial stewardship in primary health care could start with common occurring infections, selecting the most obtainable targets and those that require limited resources. For example, limiting antibiotics use for acute respiratory infections in ambulatory care, combined with recognized successful interventions to avoid treating viral conditions and utilizing narrower drugs when indicated makes these conditions priority targets for the early stages of ASPs (82, 83).



III.2 Legal Aspects of Antimicrobial Stewardship in Primary Health Care






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At the national level, legal and regulatory instruments for pharmaceuticals and health services are one of many determinants of antimicrobial use or misuse. Developing a national action plan should entail a comprehensive review of the contents and enforcement of existing legal and regulatory frameworks related to antimicrobial use. Table 8 lists legal aspects to be considered when targeting and promoting responsible use of antimicrobials. Regulating over the counter sales of antimicrobials is discussed in more detail below.

TABLE 8. ANTIMICROBIAL STEWARDSHIP PROGRAM LEGAL AND REGULATORY FRAMEWORK

LEGAL ASPECT	POSSIBLE REGULATORY MEASURE
 <p>MEDICINES REGULATION (REGISTRATION, PRODUCTION, DISTRIBUTION, ETC.)</p>	<p>Registration of medicines to ensure that only safe, efficacious good-quality medicines are available in the market and that unsafe or non-efficacious medicines are banned (e.g., fixed-dose combinations of systemic antimicrobials with symptomatic medicines, such as anti-inflammatory, or expectorants/mucolytic drugs.</p> <p>Mandatory inspections of production, distribution and dispensing facilities, to discourage counterfeiting and the sales of expired inventories.</p> <p>Banning dispensing of pharmaceuticals from illegal sources on the Internet, and unregulated donations.</p>
 <p>PRESCRIBING REGULATIONS</p>	<p>Restricting antimicrobial prescriptions based on health care setting and prescriber, such as primary health care or hospital use.</p>

 <p>DISPENSING REGULATIONS</p>	<p>Systemic antimicrobials should be sold by prescription only.</p>
 <p>EDUCATIONAL STANDARDS</p>	<p>Setting educational standards for health care professionals, and developing and enforcing codes of conduct.</p> <p>Including antimicrobial stewardship concepts in undergraduate curricula, in collaboration with academia and relevant training institutions.</p>
 <p>LICENSING OF HEALTH PROFESSIONALS</p>	<p>Strengthening the licensing processes, to ensure all practitioners meet competencies regarding diagnosis, prescription and dispensing.</p>
 <p>ETHICAL STANDARDS AND MARKETING</p>	<p>Monitoring and regulating drug promotion, so that it is ethical and unbiased; ensuring that advertising does not negatively affect antimicrobial stewardship.</p> <p>Regulating relations between pharmaceutical companies and prescribers.</p> <p>Legislating free sample distribution of antibiotics, to curb solicited distribution in the public health care system.</p> <p>Regulating online marketing and sales.</p>
 <p>REGULATION OF DONATED MEDICINES</p>	<p>Regulating product quality, regarding origin, transportation, conservation, expiration dates, etc.</p> <p>Banning haphazard donations, allowing only rigorously checked regular drugs from safe donors.</p>

To be effective, regulatory measures must be enforced and supported by pertinent authorities and the judiciary (84, 85). Regulatory interventions will likely encounter opposition, principally by drug retailers. Hence, building sufficient political support and, if possible, consensus among opposition groups before introducing regulations is essential for successful implementation (86).

At the national level, legal and regulatory instruments for pharmaceuticals and health services are one of many determinants of antimicrobial use or misuse ...



OVER-THE-COUNTER SALES OF ANTIMICROBIALS

Poor governance is significantly correlated with higher antimicrobial resistance (87). In Latin America and the Caribbean, legislation on antimicrobials is very diverse. In general, however, the law in Latin America requires that antimicrobials be sold by prescription (88). Nevertheless, over the counter sales of antimicrobials is a widespread practice, whether for lack of regulation or lack of enforcement of the law. The practice is a major driver of unprescribed antimicrobial consumption (89, 90, 91, 92). Elsewhere, a high level of regulation has significantly correlated with lower antimicrobial consumption (93).

Antimicrobial over the counter sales have been addressed in various ways by different countries in the Region. For instance, in 1999, Chile implemented strict regulation of antibiotic sales, together with a comprehensive package of related interventions (including involvement of drugstores and a public information campaign). An initial 30% decrease in antibiotic sales was reported, especially in penicillins and cotrimoxazole; however, the measures were not sustained over time, and sales increased again to near baseline levels (21). In Colombia, enforcement took effect in 2005, and was restricted to the Capital District of Bogota. Despite this geographical limitation, between the last quarter of 2004 and the first quarter of 2005, there was a significant change in sales, equivalent to 1 daily defined dose (DDD) at the national level ($P = 0.001$) (22). Venezuela introduced restrictions affecting four classes of broad-spectrum antibiotics, but no significant changes in consumption were reported. In Mexico and Brazil, regulatory changes were introduced in 2010; in both cases, overall antibiotic consumption decreased, mainly penicillins (22). In Mexico, there was an overall 12% decrease (around 1 DDD) in antibiotic consumption; the impact of the intervention was dampened by the opening of clinics adjacent to pharmacies, which bloomed after the regulation was in place (22,24).

Procedures to audit pharmacies to prevent over the counter sales of antimicrobials might follow those used to oversee the sales of psychotropic and controlled drugs; this would require human and material resources (e.g. logistics, auditors, etc.). Brazil has been following such a model since 2013 (22,24).

Countries should consider integrating such monitoring or audit procedures into their legal framework and regulation on antibiotic prescription practices in primary health care. These procedures could be managed electronically or manually, and affect all or just certain antibiotics.

LEGAL BARRIERS TO RESEARCH AND DEVELOPMENT OF NEW ANTIMICROBIAL DRUGS

The effective antimicrobial arsenal continues to decrease at an alarming rate, and new drug research and development has become even more critical (1). Pharmaceutical companies have produced few new antimicrobial drugs for regulatory approval during the last decade, in part due to the fear that research and development efforts can be undermined by the rapid emergence of resistance, and by loss of intellectual property rights. The World Trade Organization's (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights offered pharmaceutical companies better international legal rules on patent protection (94). Many WTO low- and middle-income Member States need to upgrade their legislation to fulfill the agreement's obligations. This vital aspect could be part of a national action plan dealing with AMR and of the overall strategy to battle AMR (26).

National and local (e.g., provincial, state level) legislatures need to allocate adequate funding for public sector involvement in research and development. For diseases posing large or complex problems, international regulations can play a role by structuring international cooperation through international organizations, such as the United Nations and the WHO, and partners. Critical disincentives can constrain private research and investment in new drug development, among them intellectual property protection, regulatory approval procedures, and perceived antitrust law limitations on collaborative research and development.

III.3 Education: Pre- and In-Service

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Community acquired infections, including respiratory and urinary tract infections, are a major burden to health care systems, particularly when ineffective or inappropriate treatment leads to clinical failure (95).

A clear positive association between antibiotic consumption and antibiotic resistance at the national level has been documented (96). A European Union commission recently reported that countries with higher self-reported non-prescription use of antimicrobials – such as Romania and Greece – also had higher rates of antimicrobial resistance (97). These reports make it clear that the first target of training on the proper use of antimicrobials in PHC must be the public. This issue will be addressed in another section of the present Recommendations.

It is widely recognized that pre-service and in-service training of health care workers in prescription, dispensing and use of antimicrobials is critical to address misuse and overuse of those drugs (20).

A. PRE-SERVICE EDUCATION

In low- to middle-income countries, educational competencies and curricula should be developed and/or adapted to improve training in antimicrobial use. Curricula should include modules on introduction to infectious diseases and antimicrobial resistance, common syndromes in primary health care and hospitalized patients, basic principles of antimicrobial use and infection prevention and control. The concept of stewardship at the community and hospital levels, including communication skills on how to deal with patients' expectations of prescription of antimicrobials, should also be addressed. These curricular changes should be implemented in medical, pharmacy, clinical microbiology, biochemistry, dentistry and nursing schools. Adoption of problem-based learning to progressively integrate essential concepts of pathophysiology, pharmacology, microbiology and infectious diseases should be encouraged. As previously indicated, standard treatment guidelines are an essential component of ASPs, and must be core material for undergraduate and postgraduate education (74). Standard treatment guidelines should cover key points on diagnosis, treatment and prevention of prevalent infectious diseases in different health care settings. Future prescribers should be familiar with the guidelines.

To achieve this goal, national health authorities might convene key stakeholders, such as members of academia and scientific societies, health authorities' representative of different sectors, and students' associations. Providing incentives to universities for revising and modifying their curricula (e.g., certification) may increase their interest in such an initiative (98).

B. IN-SERVICE EDUCATION

AMR and AMS core components need to be identified to train all health care workers, including prescribers and non-prescribers, in combating resistance and improper antimicrobial use. Attaining different degrees of competency will require a modular approach to education, with core components as well as additional competencies related to each specific health profession (98). In addition to the target professionals, in-service training may address public health and health services managers in leading positions or those with decision-influencing roles, as well as policy-makers.

Education is an essential component of ASP success, and ought to be part of virtually all strategies. Face-to-face training of health care workers is recommended (mainly physicians and pharmacists), especially at the beginning of their hospital careers (induction), through

classes, discussion of clinical cases and/or workshops (20). Training can begin with basic knowledge of routine utilization of clinical microbiology laboratory services; the prudent use of antimicrobials; and regular reviews of local or adopted clinical practice guidelines. Beyond the induction phase, training could take advantage of circumstances, such as the discussion of specific prescription approval processes (pre-authorization strategy), ward rounds (audits and feedback strategy), guidelines dissemination, and other such activities. It is critical to determine training priorities based on institutional needs and nuisance.

Prescription of antimicrobials in ambulatory settings is the responsibility of the PHC physician. Specific programs designed for this group include, in some circumstances, audits and control measures. Professionals responsible for implementing ASPs in outpatient services should provide regular updates on antimicrobial prescribing, AMR, and infectious diseases management. Sharing facility-specific information related to antimicrobial use helps motivate better antibiotic practices (13).

A few specific indications for antibiotics could be chosen at the beginning of in-service training in outpatient settings. Given that respiratory tract infections, urinary tract infections and diarrhea are the three leading indications for antibiotic use, specific guidelines for proper ambulatory use could be the first step in the education plan. Guidelines, written materials, and easy access to the web are useful resources.

Educational solutions increasingly need to be timely, efficient, pragmatic, high quality, consistent with the needs of the professional in a specific context, sustainable, and cost-effective. Online education has been playing a growing role in ASP training (99).

Currently, many open access e-learning courses exist, and are available to the public. One example is the PAHO/WHO Virtual Campus of Public Health (www.campusvirtualsp.org). Such open access to reliable resources must be utilized and shared, and their use promoted. E-learning tools are easy to access, and prevent duplicate efforts in designing new courses. PAHO/WHO courses are free of charge, as are many other open access training initiatives.

As pre-service and in-service education improves, national health authorities could consider individual and institutional programs for accreditation in the prudent use of antimicrobials, including topics related to AMS.

III.4 Interventions to Improve Prescription in Primary Health Care

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EVIDENCE-BASED INTERVENTIONS TO IMPROVE MEDICAL PRESCRIPTION QUALITY IN AMBULATORY CARE

Improving antimicrobial prescription practices enhances the quality of care, patient safety, and health services efficiency, all while helping to contain AMR (70, 100).

When designing ASPs for outpatient care, a range of strategies aimed at prescribers can be adapted to various settings, such as PHC clinics, private medical specialists, dental practices, and emergency rooms. Monitoring antimicrobial prescription and implementing interventions to optimize antimicrobial use are closely aligned with quality of care (70, 74, 101).

Evidence confirms that insufficient knowledge of the conditions requiring antimicrobials is not the main factor behind their inappropriate prescription. Patient expectations, uncertain diagnosis, peer pressure, and social norms play an important role, and must be addressed by PHC antimicrobial stewardship programs (102). From the patient's perspective, getting antimicrobials for an infectious disease from primary health care services is a social norm. In addition, in-training physicians are strongly influenced by the antibiotic prescribing behavior of their supervising physicians (102). However, social norms can be modulated in favor of AMS. Interest in the potential of behavioral sciences to improve these aspects of AMS is on the rise. For example, social norms feedback is a promising option. It refers to presenting information on individual prescribing practices, including that of outliers, which is useful to modify prescription practices among the latter (103).

Successful initiatives aimed at improving prescription of antimicrobials go beyond education on antimicrobial use (section III.3), and encompass strategies to change prescribers' behavior, and health care services (82, 103, 104, 105).

A gradual approach to the development and implementation of ASPs in outpatient settings could follow the steps below:

- a) Development and dissemination of standard treatment guidelines for common infections in specific clinical settings. For example, in primary health care, said guidelines would be required for common infections, such as respiratory, urinary tract, skin and soft tissue, and gastrointestinal infections. Developing

standard treatment guidelines (STGs) requires knowledge of local pathogen susceptibility, and should be periodically updated. STGs must also clearly indicate which antibiotics are not to be used due to their high cost, adverse reactions, overly broad spectrum, and/or unlikely benefit. Basic diagnostic algorithms adapted to different settings should include recommended treatment options, both first-line and alternatives, based on effectiveness and duration of therapy. STGs could also provide recommendations for non-antibiotic therapies, such as bed rest, baths, and symptomatic treatments, consistent with each clinical situation. These measures can lessen provider-patient tension during the clinical encounter, and could alleviate pressure from patients seeking an antibiotic prescription for viral infections (106). It is also recommended that STGs include brief but clear advice on how to counsel patients on the importance of preventing unnecessary use of antimicrobials, and the consequences of not doing so (107).

- b) Identification of priority conditions that require disease-specific interventions, i.e., those in which clinicians commonly deviate from standard treatments (over-prescription, under-prescription, incorrect prescription), for example, upper respiratory and urinary tract infections, asymptomatic bacteriuria, and diarrheal diseases.
- c) Identification of barriers and facilitators: When developing interventions, measures aimed at improving prescriber adherence to standard treatment guidelines must be considered. For example, faced with recommendations not to prescribe antibiotics, some clinicians may perceive a threat to their clinical autonomy. This is sometimes informally referred to as prescriber anxiety (concern of patient's well-being and satisfaction).
- d) Implement at least one evidence-based intervention: In this stepwise approach to ASP implementation, evidence-based interventions to improve antibiotic prescribing practices should be given priority.
- e) Establish a monitoring system with measurable outcomes as part of quality management. Use the resulting indicators to assess impact, and modify as needed.



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**Community acquired
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Table 9 provides a list of evidence-based interventions to improve antimicrobial prescription behavior in outpatient settings.

TABLE 9. RECOMMENDED EVIDENCE-BASED INTERVENTIONS TO IMPROVE ANTIMICROBIAL PRESCRIPTION IN OUTPATIENT HEALTH CARE SETTINGS
(71, 83, 102, 104, 106, 108, 126)

DOMAIN	OBJECTIVE/INTERVENTION
PRESCRIBER AND PUBLIC EDUCATION	See sections III.4 and III.7.
COMMUNICATIONS	<p>Improve communications to increase clinician and patient commitment to optimum antimicrobial use. For example, display a statement of public commitment to appropriate antibiotic prescription, or an open letter from clinicians to patients to be displayed as a wall poster in examination rooms. Such statements:</p> <ul style="list-style-type: none"> ✓ share the health facility's commitment and responsibility; ✓ provide consistent messages, acting as a behavioral nudge; ✓ hold all providers accountable; ✓ facilitate communication with patients about appropriate antimicrobial use. <p>Offer communications skills training to providers to address patients' concerns and manage their expectations.</p>
MANAGEMENT AND ACCOUNTABILITY	<p>Support prescribers' clinical decisions: specific information in electronic or print form, to facilitate accurate diagnoses and effective management of common conditions.</p> <p>Provide recommendations on delayed prescription: clinician's advice to use antibiotic prescriptions only if symptoms do not improve or worsen. Include this practice in standard treatment guidelines, when relevant.</p>
POINT OF CARE LABORATORY TESTING	<p>Address available point-of-care testing in standard treatment guidelines to familiarize prescribers with them.</p> <p>Include some point-of-care testing (rapid tests for streptococcal pharyngitis, C-reactive protein) at least in referral primary health care centers, and progressively increase the number of testing sites.</p>

<p>AUDIT AND FEEDBACK</p>	<p>Introduce audits (tracking) of clinician antibiotic prescribers practices, and provide feedback to individual prescribers or at facility level. This type of social norm intervention can lead to behavioral changes in prescription practices, and can also be used to assess progress in that area. Some aspects to be considered as part of audit and feedback systems are:</p> <ul style="list-style-type: none"> ✓ Select the processes to track and report. ✓ Create a data flow mechanism. ✓ Define the levels at which outcomes are reported (individual clinician or facility level), and determine comparison criteria (statistical or geographical). The preferred approach is to track and report at the individual level, and provide comparisons with top-performing peers (for example, adherence to standard treatment guidelines). <p>Types of feedback to prescribers:</p> <ul style="list-style-type: none"> ✓ E-mail ✓ Face-to-face: this approach is more time/resource-consuming, but it allows clinicians to share experiences on responsible antimicrobial use, and provides valuable inputs to the antimicrobial stewardship programs. ✓ Antimicrobial stewardship workshops: to identify and discuss opportunities to improve antimicrobial prescribing. Useful approach combining collective feedback with educational reinforcement.
<p>MONETARY INCENTIVES (PAY FOR PERFORMANCE)</p>	<p>The provision of incentives and/or compensation for improvement in antimicrobial optimal use has been successful in primary health care.</p> <p>Institutional arrangements regarding providers' payments, and an effective audit and feedback system are essential to these interventions.</p> <p>Recommended performance evaluation measures and indicators focusing on antimicrobial prescriptions can be used to evaluate:</p> <ul style="list-style-type: none"> ✓ Optimal antimicrobial selection (for example, the choice of narrow spectrum versus broad spectrum antibiotics for otitis media or pharyngitis), and treatment duration. ✓ Over-prescription for certain conditions (e.g., avoiding antimicrobial use for acute bronchitis). ✓ Overall case management (e.g., optimal utilization of the clinical microbiology laboratory, available point-of-care testing, etc.). ✓ Overall reduction in the proportion of broad spectrum antibiotics prescribed in primary care.

IMPLEMENTATION ISSUES

A global survey of hospital ASPs concluded that the scarcity of financial and human resources was a major barrier in their implementation, in addition to lack of information technology and data, and non-prioritization of AMS within institutions (20). Documented experiences on implementing ASPs in primary health care are scarce, but the same challenges as in hospitals are likely to exist. Plus, the relative autonomy of health care providers in non-hospital settings compounds the problem. To successfully implement ASPs in outpatient settings, institutional and IT support are needed.

INSTITUTIONAL SUPPORT IN HEALTH SERVICES

Ensuring the allocation and availability of financial resources for the implementation and sustainability of selected intervention is crucial to ASP implementation.

For public primary health care services, including social security, initiatives to monitor and optimize antimicrobial prescription should be embedded within institutional quality management systems. The design and implementation plan of the ASP must include mechanisms that guarantee the allocation of coordinator salaries and compensation. Further leadership support and dedicated supervision time are key factors for successful implementation.

To ensure sustainability and accountability, ASP monitoring and evaluation indicators should be linked to national quality of care programs, and targets related to health services performance evaluations must be clearly defined (100, 106).

For private sector prescribers, the situation is different from that of public sector professionals, whose prescriptions practices can be more readily assessed and corrected, if necessary. Providers in the private sector are often isolated from external reviews and recommendations. Hence, the designation of private sector ASP coordinators by the MOH is highly recommended. These coordinators must be accountable to the MOH, and preferably, selected from a department in charge of health care quality and safety in the private sector. ASP coordinators must be designated to cover different geographic areas in which to implement relevant interventions. Collaboration with professional associations is advised.

INFORMATION TECHNOLOGY SYSTEMS

Monitoring antimicrobial prescription patterns is an important function of ASPs, which can be facilitated by electronic medical records systems. Medical record information/management systems are needed to capture and to report data on: 1) duration of treatment; 2) volume of prescriptions dispensed (total volume, and break-down by therapeutic classes); and 3) adequacy of prescription, such as adherence to standard treatment guidelines. Data generated by these systems would help develop baseline data on antimicrobial prescription, and identify

problems and priorities for intervention. These data may be later used to monitor and evaluate ASP interventions. Data can be institution- or prescriber-specific, and can be used to generate feedback. A list of monitoring and evaluation indicators for ASPs is provided in section III.7.

IT systems can also be used to support prescribers' clinical decisions, for example, with diagnosis and treatment algorithms, and local anti-infective formulations, depending on the specific treatment.

RESEARCH

Interventions to improve prescriptions must be tailored to local conditions, and assessed by quantitative and qualitative research methods. For example, aggregated antimicrobial consumption data, such as the Anatomical Therapeutic Classification/Defined Daily Dose (ATC/DDD) methodology can be used to compare antimicrobial consumption among PHC institutions. Focused drug use evaluations (or drug utilization reviews) are useful to identify problems concerning the use of specific antimicrobials or the treatment of specific diseases (such as upper respiratory infections). Social sciences and behavioral studies (for example, focus group discussion, in-depth interviews, structured observation and structured questionnaires) are needed to understand the determinants of different prescription patterns for several priority conditions in PHC, as well as to determine relevant and feasible interventions. It is important to keep in mind that key targets and effective messages aimed at PHC physicians are different from those for private sector specialists. Therefore, specific research questions should be designed for each sector. Implementation research is required to assess barriers that affect intervention delivery in different health services.

III.5. Microbiology Laboratory and National Reference Laboratory

Hatim Sati, PAHO/WHO

The involvement of the clinical microbiology laboratory is essential for the success of ASPs in all health care settings. The PAHO/WHO Global Strategy for Containment of Antimicrobial Resistance “categorizes the establishment and support of clinical microbiology laboratories as a fundamental priority in guiding and assessing intervention efforts” on AMR (108). The establishment and support of microbiology laboratories can streamline testing (through rapid diagnostics), facilitate objective interpretations of antimicrobial susceptibility tests in different settings, improve quality of care for patients, and mitigate the emergence of antimicrobial resistance (44).

CLINICAL MICROBIOLOGY LABORATORY

The role of clinical microbiology laboratories is very valuable in PHC, where most antibiotics are prescribed. In PHC, providers rely on accurate and timely guidance from the CML to finalize clinical diagnoses, optimize antimicrobial therapy, improve patient outcomes (109), and reduce the risk of adverse effects and the emergence of antimicrobial resistance (40).

Beyond benefiting individual case management, cumulative antibiotic susceptibility testing data from CMLs can be used to monitor local, regional, or national resistance trends, and enable detection of circulating and emerging resistant pathogens (110). In consequence, effective integration of clinical microbiologists' input in the design and implementation of all relevant ASP interventions in health care is recommended, irrespective of setting. There is some evidence that in outpatient health care facilities laboratory testing is associated with reductions in antimicrobial use (43).

As part of ASPs, CMLs' staff is responsible for providing timely, accurate, and quality assured diagnostics. In doing so, CMLs must adhere to evidence-based guidelines (111, 112) such as those of the Clinical and Laboratory Standards Institute (45) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for sample management, and testing, and results interpretation (113). Furthermore, the ASP must encourage CMLs to follow strategies to ensure optimal antibiotic use, among them, proper specimen management, rapid diagnosis, selective reporting, summary reporting and interpretation, and stratification of cumulative data from antimicrobial susceptibility testing reports.

Proper Specimen Management

Sample quality is crucial to obtain accurate and timely laboratory diagnoses and confirmation. Accurate laboratory results decrease laboratory costs, and increase laboratory efficiency. While the selection and sampling of appropriate microbiology specimens are the responsibility of health care professionals, the CML can ensure proper sample collection, transportation, and storage. Primary care providers should consult the laboratory to ensure proper specimen management (selection, collection, transport, and storage), and an up-to-date microbiology laboratory policy manual should always be available for all medical staff (114).

Rapid Diagnosis

Prompt identification of infectious agents and their resistance mechanisms is essential for optimal antimicrobial treatment, as is the CML's access to and performance of rapid diagnostic techniques. ASPs should encourage CMLs to use rapid diagnostic tests to optimize antibiotic regimens and improve patient outcomes, but not in lieu of conventional cultures (111). When using rapid diagnostic tests, the results should include guidance on their interpretation.

Selective Reporting

The importance of CMLs in providing selective reports on antimicrobial susceptibility was already discussed in section II.5, above. For PHC, selective reporting must also incorporate evidence-based recommendations and guidelines, such as those from the Pan-American Infectious Diseases Association or API (37), IDSA (40), and CLSI (M39-A) (115). The impact of antimicrobial susceptibility testing selective reporting of prescribing patterns and outcomes should be reviewed periodically (annually), and selective reporting updated.

Reporting and Interpretation

Delays and inappropriate interpretation of laboratory results are significant causes of suboptimal antibiotic use, and CMLs should ensure the proper flow and expediency of results. Pathogen identification and susceptibility testing results are best reported to the physician in a clear format to encourage narrow/optimal drug selection. ASPs should stimulate all CMLs to utilize published guidelines for proper reporting of antibiograms.

Stratification of Cumulative Data from Antimicrobial Susceptibility Testing Reports

Cumulative antimicrobial susceptibility testing data can be used to monitor the impact of outpatient prescription practices related to resistance, and to develop empiric treatment guidelines (110). ASPs should prefer stratified (e.g., by age, location, specimen, isolate type, and clinical relevance) cumulative antimicrobial susceptibility data over non-stratified data to develop guidelines for empiric therapy. Limited evidence exists on the impact of stratification on empiric therapy in PHC. Nevertheless, important information about differences in susceptibility profiles and patterns of resistance can be obtained from stratifying susceptibility data at the institutional level, as well as at local, regional, and national levels (43).

Ongoing training and education for clinical microbiology laboratory personnel on microbiology laboratory techniques, equipment, and appropriate and safe specimen management.



CLINICAL MICROBIOLOGY LABORATORY NETWORK

Clinical microbiology laboratory reports on microorganism identification and antimicrobial susceptibility testing are essential for antimicrobial therapy decisions. Therefore, accessible CMLs that can carry out timely pathogen identification and in-vitro antimicrobial testing and reporting are needed.

When establishing a regional network, consider CML geographic location to ensure that cities, provinces, and regions are well covered. The network should preferably include public and private laboratories. It is very important that CML services be readily and locally accessible to health care providers in primary health care. Demographic and socioeconomic considerations should also determine the establishment of CMLs, to ensure support trend monitoring across diverse settings. This will allow the network to inform STG based on the specific needs of each location.

In Latin America and the Caribbean, the actual number of participating laboratories and their geographic distribution depends on the national CML infrastructure, and the ability of these laboratories to perform timely pathogen identification and in-vitro antimicrobial susceptibility testing. On-site laboratory capacity is not essential, if the site can store and quickly transport samples to the regional reference laboratory (116). Laboratories without testing capacity need to ensure proper specimen management, including sample storage at optimal recommended temperatures (with generators and systems in place to accommodate standard temperatures and changes in access to electricity). Prompt sample transportation from these sites is a must, as is ensuring required temperatures during transportation.

All primary health care facilities should be able to forward samples to a CML, even if the laboratories that serve them are in a secondary-level facility. Some specialty outpatient clinics may be considered for certain priority pathogens (e.g., sexually transmitted infections clinics for *Neisseria gonorrhoeae* AMR surveillance). PHC physicians should be encouraged to seek the services of those clinics for their patients' health care.

The number and capability of CMLs can vary widely among regions and countries. Laboratories with adequate infrastructure and core capacity for AMR surveillance for priority pathogens (primary sites) must be identified and supported. In turn, those primary sites can support the development of best practices in secondary CML sites, with the long-term objective of building a comprehensive network of CMLs with core capacities for surveillance, and to support ASPs. One key issue here is the

time it takes the reference laboratory to report results to the original site of care, so all measures to shorten this process (e.g. mobile phone communications and alerts, online reports) should be implemented and closely monitored. When results are not timely communicated, PHC physicians tend to dismiss the CML's usefulness.

The performance quality of the CML network should be safeguarded by internal and external quality control systems. Each participating laboratory must follow several standard assessment procedures to guarantee the quality of test reagents and test performance (116).

NATIONAL REFERENCE LABORATORY

National health authorities must identify at least one national public health laboratory with adequate infrastructure and capacity for antimicrobial resistance surveillance and characterization to serve as the national reference laboratory (NRL) for AMR surveillance. The designated NRL will oversee the external quality assurance program that ensures CMLs' performance according to standards (116). National reference laboratories should also participate in these laboratories' performance evaluations.

National reference laboratories should be coordinated by the national health authority that serves as technical liaison between AMR surveillance and ASPs. Said national authority should also provide technical, logistic, and financial support. Coordination of the national reference laboratory and CMLs at national level allows standardization of data collection, and ensures that antimicrobial susceptibility testing and surveillance protocols are consistent with national and international standards (WHO manuals, CLSI or EUCAST guidelines).

Following is a summary of the functions expected of national reference laboratories:

- » Coordination and promotion of external quality assurance programs for clinical laboratories, including training, consultation, certification and proficiency testing.
- » Ongoing training and education for clinical microbiology laboratory personnel on microbiology laboratory techniques, equipment, and appropriate and safe specimen management.
- » Ad hoc confirmation of identification of pathogens under surveillance (confirmation to the species level, MICs).

- » Performance of specialized testing: providing high level reference diagnostics, including molecular testing.
- » Development and dissemination of recommendations for internal and external quality assurance.
- » Establishing national alert rules for strain confirmation.
- » Timely laboratory verification of unusual isolates, including confirmation and characterization (phenotypical antibiotic susceptibility testing).
- » Strengthening rapid response to outbreaks through timely testing and identification of causal agents, and providing laboratory support during outbreak investigation, including epidemic alerts, response and prevention, and monitoring.
- » Providing supplies and consumables (such as reagents) to CMLs during emergency situations.
- » Monitoring epidemiological trends to detect shifts, and ensuring rapid analysis and dissemination of laboratory information.
- » Technology development/acquisition, and transfer.
- » Data collection, compilation, analysis, and report generation and dissemination at national, regional or global level, as required.
- » Establishing standards, and advocating for public and private clinical microbiology laboratory services.
- » Participating in subregional, regional, and global antimicrobial resistance networks.
- » Research and development.
- » Providing scientific and managerial leadership to develop public health policy around AMR surveillance and stewardship.

National reference labs must have the capacity to collect CML data and verify its quality. Laboratory staff must be trained in data collection, analysis and reporting, and updating of epidemiological, clinical and laboratory data, including the capacity for basic demographic analysis. If a national reference laboratory is not yet nationally available, collaboration can be temporarily established with an appropriate foreign institution.

Analyses and updates of antimicrobial susceptibility patterns, circulating pathogens, and emerging resistance alerts or outbreaks must be widely and timely disseminated to all network and ASP participants at all levels (Ministry of Health, primary health care providers, pharmacists, clinical microbiologists, facility managers, etc.). This can be done via website, intranet, mass email, or short message services. This is especially important for public health updates/alerts. Alerts are often communicated by national reference laboratories, and are generated by critical AMR trends, or incidents of public health importance involving AMR pathogens. This approach to surveillance and timely reporting to health authorities and providers at all levels usually deals with emerging public health events, and enables decision-making to prevent and control the event's spread into communities, health care services, and countries.

III.6 Public Information Campaigns

Rolando Cedillos, Hospital Rosales, San Salvador, El Salvador

Objective 1 of WHO's Global Action Plan on Antimicrobial Resistance (26) calls on Member States to raise awareness of AMR, and to encourage the use of antimicrobial agents only when indicated. Evidence indicates that public information campaigns promoting responsible antibiotic use may be associated with reductions in overall antibiotic use in Europe (117). Unfortunately, in Latin America and the Caribbean such efforts have been scarce. Action by national health authorities to raise public awareness on the issue is crucial (118, 119).

In designing and/or conducting public awareness campaigns, governments should involve key stakeholders, such as professional societies of infectious diseases, microbiology, PHC physicians, pharmacy, and community members. Some surveys show that these interventions should also include the participation of members from other sectors who have been absent or not always involved in these efforts, for example, communications specialists, patients or patient interest groups, psychologists and sociologists (118).

Box 4, below, provides examples of key messages for public awareness campaigns on optimal use antimicrobials.

BOX 4. KEY MESSAGES FOR PUBLIC AWARENESS CAMPAIGNS ON OPTIMAL USE OF ANTIMICROBIALS

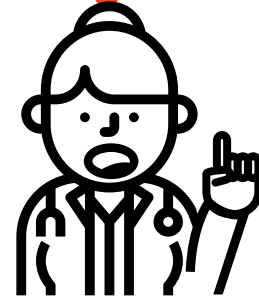
Key messages for places where surveys show that most people believe that a cold or flu can be treated with antibiotics. The message could read:

“ANTIBIOTICS DO NOT WORK AGAINST COLDS, FLU, OR OTHER VIRUSES. THEY ONLY WORK AGAINST BACTERIA.”

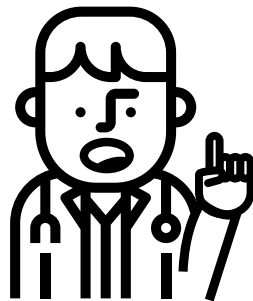
“ANTIBIOTICS CAN BE HARMFUL TO THE BODY.”

Other key messages:

- “MISUSE AND OVERUSE OF ANTIBIOTICS CAUSE RESISTANCE, SO **THEY WILL BE USELESS WHEN WE REALLY NEED THEM.**”
- “IF WE USE ANTIBIOTICS INCORRECTLY WE WILL LOSE THEM; **THEY WILL BECOME INEFFECTIVE.**”
- “**ANTIBIOTIC RESISTANCE** IS AN IMPORTANT PROBLEM THAT **AFFECTS EVERYBODY.**”



Key messages aimed at antimicrobial self-medication behavior/practices:



“DO NOT BUY OR USE ANTIBIOTICS WITHOUT A PRESCRIPTION.”

Surveys have shown that only few campaigns mention that antibiotics have side effects, and even fewer, that antibiotics can interfere with other drugs a patient may be taking (118). In Latin America and the Caribbean, it is particularly important to address self-medication. Cultural context and local adaptation of slogans are essential to achieve the best impact in each individual country. Messages too complex to be assimilated by the public should be avoided. Campaigns can be delivered by television, radio, pamphlets, brochures, leaflets, posters, letters to stakeholders, print media, billboards, public transportation signs, and signage in physicians' offices, clinics, and pharmacies. Pharmacists should be involved in message delivery. For example, a message indicating that *the flu* cannot be treated with antimicrobials could be transmitted by the pharmacist to patients seeking to buy antimicrobials. More modern methods, including online information dissemination through websites, social media channels, videos, etc. should be an integral part of any public awareness campaign. Interviews with persons who have had adverse reactions to antimicrobial agents taken without indication might be of benefit. If influenza vaccination is available, identify opportunities to get the public vaccinated.

Beyond the public, messages targeting specific population groups, like parents and health care professionals responsible for prescribing antibiotics to children and adolescents could increase the impact of campaigns.

Studies have demonstrated that successful awareness campaigns transmit carefully designed and simple key messages; target a wide audience, such as patients, their families and health care workers; engage physicians and other health care professionals early in the campaign and jointly design key messages; use mass media and social media, and continuously reiterate key messages (119). CDC's Get Smart campaign can be a resource for such materials (<https://www.cdc.gov/antibiotic-use/week/educational-resources/resources.html>).

It is important that campaign impact evaluations measure, at least, public knowledge, before and after any intervention. Indicators such as antibiotic consumption (e.g., the amount purchased from or dispensed by pharmacies), changes in public and health care professional attitudes and even antimicrobial resistance rates are also advisable.



A crucial aspect of establishing a monitoring and evaluation system is to define adequate indicators. The main elements to consider when selecting a set of indicators are the availability of data and the ease or difficulty of obtaining it, both at the national and health-care facility level ...

III.7 Monitoring and Evaluation of Antimicrobial Stewardship Programs in PHC

Anahi Dreser Mansilla, Instituto de Salud Pública, Cuernavaca, México

Outcome evaluation of interventions is essential for all ASPs. Furthermore, within quality management systems, monitoring is needed to detect problems, to implement corrective measures, and to ensure that satisfactory quality levels are maintained. The establishment of ASPs at the national level should begin with a qualitative and quantitative situation analysis to determine the types and extent of inappropriate antimicrobial use, and their determinants. Baseline information is needed to understand and address the latter (84). Key indicators of these three spheres should be chosen to monitor and evaluate ASP implementation at the national level. Likewise, improving prescribing behavior within PHC facilities requires a situation analysis and routine follow-up to monitor the types, magnitude and determinants of antimicrobial prescribing by health professionals (see section III.4).

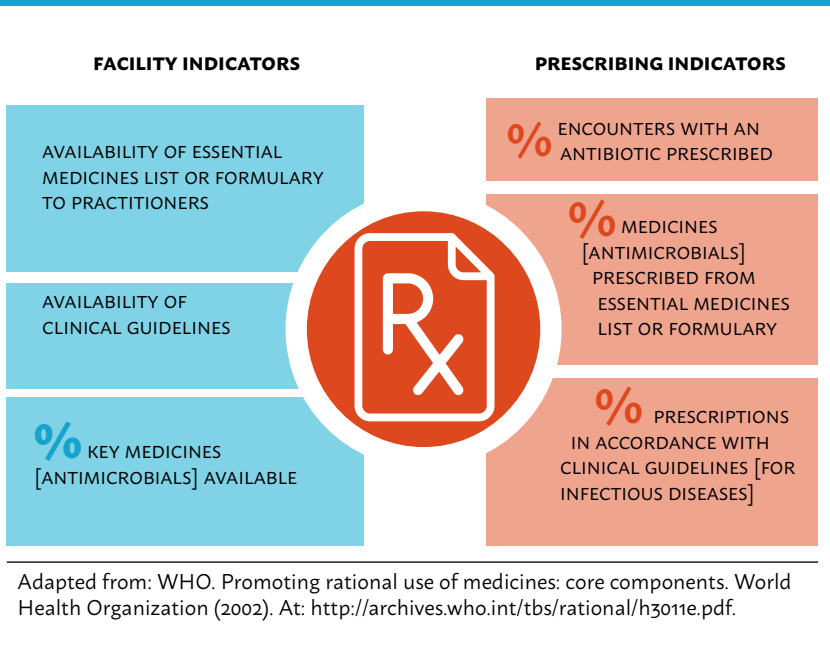
INDICATOR SELECTION

A crucial aspect of establishing a monitoring and evaluation system is to define adequate indicators. The main elements to consider when selecting a set of indicators are the availability of data and the ease or difficulty of obtaining it, both at the national and health-care facility level. One should start by asking what can be evaluated with the available data, knowing its limitations (120), and what is the usefulness of the indicator for decision-making.

Some ASP-relevant indicators have been extensively used to identify general prescribing practices and quality of care problems at PHC facilities, such as those proposed by the WHO and the International Network for the Rational Use of Drugs (INRUD) (84) (Box 5). Similarly, health care facilities or social security institutions may already have in place health care quality management systems that include some data related to antimicrobial prescriptions. Compiling and analyzing data using these or other relevant indicators already in place in national health services could provide a good start.

New indicators that measure stewardship intervention outcomes specifically could be progressively added as ASPs are implemented and monitoring and evaluation systems are developed. An early selection of specific ASP indicators might be based on existing international guidelines, keeping in mind that those indicators must be adapted for each country and health facility. In addition, some indicators will be standard for regional and global-level reporting (121).

BOX 5: SELECTED WHO/INRUD DRUG USE INDICATORS RELEVANT FOR ASP IN PRIMARY HEALTH CARE FACILITIES



OUTPUT, OUTCOME AND IMPACT INDICATORS

ASP monitoring and evaluation is a field still in development. In general, ASP indicators measure output, outcome, and impact. Output indicators reflect what the ASP will do or deliver (e.g., availability of standard treatment guidelines in health care facilities; the number of education interventions in a given period). Outcome indicators measure the quantity and quality of antimicrobial use, and impact indicators refer to the long-term goals of the ASP and the consequences of antimicrobial use, such as the prevalence of resistant pathogens, and mortality from antimicrobial resistant infections. Indicators can also be classified by component of the primary health care ASP. Table 10 lists examples of output and outcome indicators for each ASP component that countries could use to choose the most appropriate for each context.

Output indicators. Output indicators measure ASP deliverables, i.e., results that are attributable to the program itself. These are short term (< 5 years) indicators useful for monitoring progress at the national or institutional level. Output indicators measure determinants or reasons of inappropriate antimicrobial use, and hence, interventions and strategies included in the ASP at the national and institutional level.

Outcome indicators. Outcome indicators are intended to measure changes achieved by the ASP by measuring prescriber behaviors. They are central to ASP monitoring and evaluation at the national level. At the institutional level, these indicators are essential for quality management systems. Two broad sets of indicators are recommended (Table 10):

- » Quantity metrics: Determine the average amount of antimicrobials being consumed, and their cost, in a given institution, or at national and sub-national levels in a given period.
- » Quality indicators: Are measurable elements of performance, which can be used to assess the quality - and changes in the quality - of care provided.

Regarding quantity metrics, the Anatomical Therapeutic Classification (ATC)/Defined Daily Dose (DDD) method has been widely used in antimicrobial consumption studies. The unit of analysis DDD per 1,000 inhabitants per day based on retail sales has been used to measure antibiotic consumption in ambulatory care, as well as the impact of AMS interventions at the national level (24). A major advantage of this method is that it allows benchmarking within and among institutions. However, caution should be exercised when comparing institutions of different case mixes, for example, with higher proportion of elderly or pediatric patients. Another advantage is that it can be calculated in the absence of computerized pharmacy or medical records by using purchasing data (122). Other quantity metrics commonly used are the number of antibiotic prescriptions per physician contact, and the volume of broad spectrum antibiotics (such as cephalosporins and quinolones) as a proportion of all antibiotics prescribed.

Quality indicators are, arguably, the ideal measures for assessing antimicrobial consumption appropriateness. However, still much discussion is going on regarding their applicability. Care consistent with standard treatment guidelines has been widely recommended as a key quality indicator; however, it is important to consider that most STGs have been developed without considering antimicrobial stewardship principles, so they must be revised to assure their validity when measuring appropriateness (75,123).

Quality indicators are key to quality management systems. Coding infectious disease diagnoses (requiring an antibiotic or not) in PHC patient records, and linking these codes to antibiotic prescriptions should be promoted in all settings, since it is a prerequisite for audit and feedback as well as for pay-for-performance interventions. However, periodic assessments of diagnosis coding accuracy are also necessary, as misdiagnosis is a frequent driver of unnecessary antibiotic prescription (70,123). A description of national targets for reducing unnecessary antibiotic use in outpatient settings for specific health conditions, such as acute respiratory infections, is provided elsewhere (124).

ASP impact indicators. These indicators measure progress toward long term goals to which ASPs may contribute, but not control. Of course, the primary reason to implement AMS is increasing antimicrobial resistance; accordingly, AMR is an important metric of the impact of ASPs. However, given the many other drivers of AMR in the community (for example, non-human antibiotic use or co-interventions), it is not an adequate measure of an ASP's success (122).

ASPs must also consider patient outcome measures, such as infectious diseases related mortality, complications or cure, that allow the assessment of intended and unintended consequences of changes in prescription behaviors. Certain health care systems may also be able to track and report complications of antibiotic use (e.g., *C. difficile* infections, drug interactions, and adverse drug events). However, at the individual or facility level, smaller sample sizes could make these measures less reliable or useful (70).

TABLE 10. EXAMPLES OF OUTPUT AND OUTCOME INDICATORS FOR EACH ANTIMICROBIAL STEWARDSHIP PROGRAM COMPONENT IN PRIMARY HEALTH CARE

ANTIMICROBIAL STEWARDSHIP PROGRAM COMPONENT	INDICATOR
REGULATION OF ANTIMICROBIAL COMMERCIALIZATION	<ul style="list-style-type: none"> » Output » Regulations are introduced and enforced to allow systemic antibiotic sales only with medical prescription » Outcome » Proportion of systemic antibiotics sold with medical prescription
MEDICAL EDUCATION (PRE-SERVICE)	<ul style="list-style-type: none"> » Output » Health sciences schools (medicine, dentistry, nursing) include ASP concepts in their curricula » Outcome » Percentage of medical school graduates who know the antibiotic of choice for the treatment of common infections in PHC
IMPROVED PRESCRIPTION BEHAVIOUR IN AMBULATORY CARE	<ul style="list-style-type: none"> » Output » Health care institution develops an audit and feedback program » Health care institution has targets for antibiotic prescribing, with systems or incentives to encourage appropriate behaviors » Country has access/watch/reserve antibiotic categories in STG and essential medicine list » Outcome » Percentage of antimicrobials prescribed in line with STGs » Average number of antibiotic prescriptions per 1,000 inhabitants per year; proportion of health care workers who prescribed a restricted antibiotic » Watch and reserve antibiotic use compared to access antibiotics; or ratio of sales of watch: reserve antibiotics

<p>SURVEILLANCE OF ANTIMICROBIAL RESISTANCE IN THE COMMUNITY LINKED WITH INFORMATION DISSEMINATION FOR PRESCRIBERS</p>	<ul style="list-style-type: none"> » Output » Country has database for collecting and reporting resistance data in PHC » Country facilitates information technology in geographically distributed primary, secondary and tertiary health care facilities » Outcome » Country has reported and published AMR surveillance data » % of hospitals where AMR data are periodically provided to local hospital-based physicians at regional or local level » Frequency of STG updates based on AMR rates change during the most recent 2 to 4 years
<p>GENERAL POPULATION EDUCATIONAL CAMPAIGNS</p>	<ul style="list-style-type: none"> » Output » Government-supported antimicrobial awareness campaign(s) undertaken by target group » Outcome » % of public who knows it is inappropriate to use antibiotics for common cold or viruses » % of public who self-prescribed antimicrobials during the most recent year

Source: PAHO-FIU (2017). Monitoring and Evaluation of the Global Action Plan on Antimicrobial Resistance (AMR): Regional Expert Consultation on Monitoring and Evaluation of AMR Interventions. https://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=39279

Several international initiatives have recently been developed to validate quality indicators and quantity metrics to monitor antibiotic use as part of national ASPs. Table 11 lists a compilation of relevant indicators for monitoring and evaluating ASPs in outpatient settings, reflecting the concept of *responsible use of antibiotics* as proposed by the DRIVE AB project (125). Some countries (largely high-income) have already established national PHC indicators with clear targets. Many of them are linked to incentives (such as public reporting, premiums and pay-for-performance [P4P] systems in PHC, to encourage implementation (123). Most of these indicators, however, were devised for high-income countries, and some of them might not be relevant for or feasible in low- to middle-income settings. A thoughtful discussion and agreement involving monitoring and evaluation experts and a variety of ASP stakeholders is of utmost importance for the selection of indicators in every country in Latin America and the Caribbean.

TABLE 11. INDICATORS FOR MONITORING AND EVALUATION OF ANTIMICROBIAL STEWARDSHIP PROGRAMS (ASP) IN OUTPATIENT SETTINGS

QUALITY INDICATORS FOR OUTPATIENT SETTINGS	
ASP OUTCOME INDICATORS	ASP OUTPUT INDICATORS
OQI-1 Antibiotics should be prescribed for (most) bacterial infections (e.g. acute pneumonia, urinary tract infections).	OQI-11 Antibiotics from the list of essential antibiotics should be available in health facilities that dispense antibiotics.
OQI-2 Antibiotics should not be prescribed for (most) viral infections or self-limiting bacterial infections (e.g. acute bronchitis, influenza, acute otitis media in patients > 2 years of age).	OQI-12 Key antibiotics should not be out of stock in health facilities that dispense antibiotics.
OQI-3 Outpatients should receive antibiotic therapy in compliance with guidelines; this includes, but is not limited to indication, choice of antibiotic, duration, dose and timing.	OQI-13 Antibiotics in stock should not be available beyond the expiry date.
OQI-4 Some antibiotics should be rarely prescribed.	OQI-14 Antibiotics that are dispensed to outpatients should be adequately labeled (patient name, antibiotic name, when antibiotic should be taken).
OQI-5 Acute upper respiratory infections and bronchitis should not be treated with antibiotics within the first three days of disease onset, unless there is documented indication for treatment.	OQI-15 Antibiotics should be adequately conserved and handled in health facilities.
OQI-6 Outpatients with acute tonsillitis/pharyngitis should be tested for group A streptococcal infection to decide whether to indicate antibiotics.	OQI-16 Health facilities should keep adequate records of dispensed key antibiotics.
OQI-7 Outpatients with acute tonsillitis/pharyngitis and positive group A streptococcal diagnostic test should be treated with antibiotics.	OQI-17 A copy of the essential antibiotics list should be available in health facilities.
OQI-8 Antibiotics for acute tonsillitis/pharyngitis should be withheld, discontinued or not prescribed if outpatient diagnostic test (rapid antigen test or throat culture) is negative for group A streptococci.	OQI-18 Standard antibiotic treatment guidelines should be available in health facilities.
OQI-9 Prescribed antibiotics should be chosen from an essential list/formulary.	OQI-19 Health facilities should have access to the summary of product characteristics of prescribed antibiotics, written in a local language.
OQI-10 Possible contraindications should be considered when antibiotics are prescribed.	OQI-20 Antibiotics should not be sold without prescription.

QUANTITY METRICS FOR OUTPATIENT SETTINGS

ASP OUTCOME INDICATORS

OQM-1 Defined Daily Doses (DDD) per defined population

OQM-2 Treatments/courses per defined population

OQM-3 Treatments/courses per physician contact

OQM-4 Prescriptions/defined population

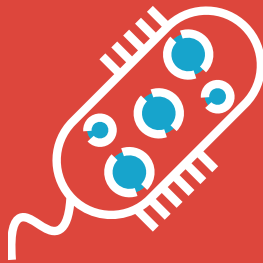
OQM-5 Prescriptions/physician contact

OQM-6 Seasonal variation of total antibiotic use.

Modified from: Vlahovic-Palcevski V. DRIVE AB: Reinvestment in R&D and responsible antibiotic use (2014). Available at:

http://drive-ab.eu/wp-content/uploads/2014/09/WP1A_Final-QMs-QIs_final.pdf





Annex

Clinical microbiologic
laboratory additional
tools

TABLE I-1. SUGGESTIONS FOR CASCADE REPORTING				
MICROBE DETECTED	ANTIMICROBIAL SUSCEPTIBILITY TESTING PHENOTYPE	ANTIMICROBIALS TO REPORT	ANTIMICROBIALS TO BE HIDDEN OR RESTRICTED	COMMENTS
METHICILLIN SUSCEPTIBLE <i>Staphylococcus aureus</i>	Susceptible to oxacillin	Oxacillin, erythromycin, clindamycin, trimethoprim/ sulfamethoxazole	Tigecycline, daptomycin, vancomycin, ceftaroline linezolid, ciprofloxacin	Consider reporting options in case of beta-lactam allergy. Vancomycin should be reported in case of type 1 hypersensitivity reactions or allergy to cephalosporins.
<i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Proteus mirabilis</i>	Pansusceptible	Beta-lactam/ beta-lactamase inhibitors, cephalosporins, aminoglycosides, trimethoprim/ sulfamethoxazole, fosfomicin, nitrofurantoin	Monobactams, carbapenems, colistin, tigecycline, ciprofloxacin, ceftazidime/ avibactam, ceftolozane/ tazobactam	Consider exceptions in cases of septic shock or allergy. Cefazolin should be used to predict oral cephalosporins activity in uncomplicated urinary tract infection (UTI) treatment. Fosfomicin-trometamol and, nitrofurantoin, should be reported in lower UTI only.
CHROMOSOMAL AMPC PRODUCERS: <i>Enterobacter</i> , <i>Serratia</i> , <i>Proteus vulgaris</i> , <i>Morganella</i> , <i>Providencia</i> , <i>Citrobacter</i> , <i>Aeromonas</i> , <i>Hafnia</i> , <i>Edwardsiella</i> , <i>Pantoea</i> , <i>Klebsiella aerogenes</i>	Inducible AmpC	Cefepime, piperacillin/ tazobactam carbapenems, ciprofloxacin trimethoprim/ sulfamethoxazole, aminoglycosides	First, second and third generation cephalosporins, aminopenicillins, aminopenicillins plus inhibitors, tigecycline, colistin, ceftazidime/ avibactam, ceftolozane/ tazobactam	Consider exceptions in cases of septic shock or allergy
<i>Pseudomonas aeruginosa</i>	Pansusceptible	Piperacillin/ tazobactam, cefepime, ceftazidime, ciprofloxacin, tobramycin, aztreonam	Meropenem, doripenem, colistin, ceftolozane/ tazobactam	Consider exceptions in cases of septic shock or allergy

Adapted from: Guía para la implementación de un programa de optimización de antimicrobianos PROA a nivel hospitalario. API 2016. Available at: http://www.apinfectologia.com/wp-content/uploads/2018/01/manual-PROA_2016.pdf

ALERT SYSTEMS FOR SUSCEPTIBILITY REPORTS IN MULTI-DRUG RESISTANT BACTERIA AND INFECTIOUS DISEASE CONTROL:

Clinicians currently face many challenges when interpreting and using antibiotic susceptibility reports at the time of prescribing. In some microorganism/drug combinations there are mechanisms that clearly confer high level of resistance, such as in *vanA/vanB* enterococci. In these cases, errors in susceptibility reporting are rare. However, other mechanisms with significant clinical impact may not always be evident when relying MIC testing results, for example, when MICs right below the susceptible breakpoint (i.e., ESBLs, OXA-type carbapenemases). Moreover, without correct identification, multidrug-resistant bacteria can disseminate throughout the hospital causing outbreaks which are associated with high mortality and cost. The spread of such microorganisms can happen by horizontal gene transfer (HGT) via plasmids or transposons, or clonal dissemination from the initial isolate.

One approach to prevent inappropriate treatment is to include prescription alerts for certain microorganism/drug/mechanism combinations. These alerts serve as warnings to avoid the use of antimicrobials which could select for specific resistance, and to guide the implementation of contact precautions, necessary. Table I-2 provides examples/suggestions on these issues.

TABLE I-2. EXAMPLE OF ALERT REGARDING TREATMENT OF CERTAIN BACTERIAL INFECTIONS, SELECTED PHENOTYPES, DETECTION METHODS AND RECOMMENDATIONS

RESISTANT PHENOTYPE	Molecular basis	Usual pattern in antimicrobial susceptibility testing results	Detection methods	Footnote
METHICILLIN-RESISTANT <i>Staphylococcus aureus</i> (MRSA)	<i>mecA/mecC</i>	Oxacillin resistance	Oxa MIC, FOX MIC, FOX DD, PCR, latex for PBP2-a	Oxacillin resistant <i>S. aureus</i> is considered resistant to other β -lactam agents, except for cephalosporins with anti-MRSA activity. Contact precautions are advised.
EXTENDED SPECTRUM BETA-LACTAMASE (ESBL)	<i>bla-CTX-M, bla-SHV, bla-TEM</i>	Resistance to cephalosporins, monobactams and beta-lactam/beta-lactamase inhibitors	BMD, E-test or DD using clavulanic acid, chromogenic agars, PCR.	Extended spectrum beta-lactamase detected. The use of cephalosporins is not recommended. The use of piperacillin/tazobactam should be advised by infectious diseases specialist.
CHROMOSOMAL CEPHALOSPORINASE	<i>AmpC genes</i>	Resistance to cephalosporins other than cefepime, monobactams and beta-lactam/beta-lactamase inhibitors	Boronic acid, cloxacillin, PCR.	Chromosomal/plasmid AmpC detected. Use of 1st, 2nd and 3rd generation cephalosporins is not advised.

CARBAPENEMASE-PRODUCING <i>Enterobacteriaceae</i> (CPE)	KPC, NDM, VIM, OXA-48, GES,	For KPC and MBLs (VIM, NDM) resistance to cephalosporins and carbapenems. For OXA-48 resistance to carbapenems	MHT, mCIM, boronic acid, EDTA, Carba NP, Blue Carba, PCR	Carbapenemase-producing <i>Enterobacteriaceae</i> . Combined therapy, contact precautions, and infectious disease consulting is advised
VANCOMYCIN-RESISTANT <i>Enterococci</i> (VRE)	VanA/ VanB	Vancomycin and teicoplanin resistance	E-test, BMD, DD, PCR, agar dilution	Vancomycin resistant <i>Enterococcus</i> . Combined therapy, contact precautions and ID consulting is advised.
CARBAPENEM RESISTANT <i>Acinetobacter spp</i>	OXA-23 OXA 58 VIM NDM KPC	Resistance to carbapenems and ceftazidime	Carba NP; PCR, EDTA inhibition, BMD, DD, E-test	Carbapenem resistant <i>Acinetobacter</i> . Combined therapy, contact precautions and ID consulting is advised.
POLYMYXIN RESISTANT GRAM-NEGATIVE BACILLI	mcr genes MgrB mutations CrrA mutations	Resistance to colistin in <i>Escherichia coli</i> , <i>Klebsiella aerogenes</i> , <i>Enterobacter cloacae</i> , <i>Raoultella ornithinolytica</i> , <i>Acinetobacter</i> , <i>Pseudomonas</i>	Polymyxin B NP, BMD, PCR	Polymyxin resistant Gram-negative bacilli. Contact precautions and infectious diseases consulting is advised.

BMD: broth micro dilution; DD: disk diffusion; EDTA: ethylenediaminetetraacetic acid; MHT: modified Hodge test; Mcim: modified carbapenem inactivation method; PCR: polymerase chain reaction.

RECOMMENDATIONS FOR TESTING AND REPORTING POLYMYXINS

Polymyxins (colistin and polymyxin B) are drugs used as salvage antimicrobials (many times in combination with other antibiotics) for infections caused by multi-drug resistant Gram-negative bacteria, mainly carbapenemase producers and multi-drug resistant *Acinetobacter baumannii*. These drugs target lipid A in the lipopolysaccharide to cause bacterial lysis. Unfortunately, there are some issues regarding testing and clinical interpretation of AST results with these drugs. Following are some recommendations for testing and reporting polymyxins based on current Clinical and Laboratory Standards Institute (CLSI) guidelines (45):

- » Colistin testing and reporting is necessary for organisms which test resistant to carbapenems using current CLSI breakpoints (Table 1-3) or isolates with positive phenotypic test for carbapenemases (mCIM, Carba NP, Blue Carba, etc.), or with positive molecular test. For non-fermenting Gram-negative rods, additional testing for resistance to ceftazidime must be done.

- » Colistin should be tested using a validated broth microdilution method (BMD). Do not use polysorbate 80 (tween) or other surfactant to treat polystyrene plates.
- » Do not use agar methods like disk diffusion, agar dilution or gradient test (E-test or similar).
- » The species *Serratia*, *Morganella*, *Providencia*, *Proteus*, *Hafnia*, *Burkholderia*, *Vibrio*, and *Edwardsiella* are intrinsically resistant to colistin, therefore, do not test nor report colistin for these isolates.
- » For *Enterobacteriaceae*, use the current CLSI epidemiological cut off values.
- » For non-fermenting Gram-negative isolates (*Pseudomonas* and *Acinetobacter*) use current CLSI breakpoints (M100S - 27th Edition).
- » For *Enterobacteriaceae* isolates which test resistant (MICs ≥ 4 $\mu\text{g/ml}$), consider performing polymerase chain reaction (PCR) test for MCR genes. Include a footnote in the antimicrobial susceptibility test result to advise consultation with infectious diseases specialist, and contact precautions.
- » Include quality control strains to guarantee accurate results for colistin: *Escherichia coli* ATCC 25922 (MIC range 0.25-2 $\mu\text{g/ml}$) and *Pseudomonas aeruginosa* ATCC 27853 (MIC range 0.5-4 $\mu\text{g/ml}$).

TABLE I-3. 2017 CLSI BREAKPOINTS AND EPIDEMIOLOGICAL CUT-OFF VALUES (ECVs) FOR COLISTIN IN GRAM-NEGATIVE RODS

MICROORGANISM	CLINICAL MIC BREAKPOINTS ($\mu\text{G/ml}$)			EPIDEMIOLOGICAL CUT OFF VALUES ($\mu\text{G/ml}$)		
	S	I	R	S	I	R
<i>Pseudomonas aeruginosa</i>	≤ 2	-	≥ 4	-	-	-
<i>Acinetobacter baumannii</i>	≤ 2	-	≥ 4	-	-	-
<i>Enterobacteriaceae</i> *	-	-	-	≤ 2	-	≥ 4

*Applies only to *Escherichia coli*, *Klebsiella pneumoniae*, *Raoultella ornithinolytica*, *Enterobacter cloacae*, *E. aerogenes*.

Some rapid methods can detect resistant markers (carbapenemase genes, *mecA*, *VRE*, other); their presence usually correlates well with antimicrobial susceptibility testing results. Sometimes, however, there is a mismatch between the presence or absence of resistant genes and susceptibility results. In those cases, CLSI recommends using a third method to confirm the results, or to interpret susceptibility results as resistant when a resistant gene is present, despite MIC results (1,126).

TABLE I-4. RAPID DIAGNOSTIC MICROBIOLOGY PLATFORMS

METHODS WITHOUT AMPLIFICATION (GROWTH DEPENDENT)	METHODS WITH AMPLIFICATION (GROWTH DEPENDENT)	DIRECT SAMPLE DETECTION (GROWTH INDEPENDENT)
PNA-FISH	BD GeneOhm	Septifast
QUICK-FISH	Xpert MRSA-	Septitest
VERIGENE BC GP	Xpert Carba	T2 Candida magnetic resonance
VERIGENE BC GN	FilmArray BC-ID.	FilmArray /GI, CNS, respiratory, BCID

CUMULATIVE ANTIMICROBIAL SUSCEPTIBILITY REPORT (CASR)

Often referred to simply as “antibiograms,” CASRs have many uses, including, but not limited to, helping prescribers select effective therapy when culture results are pending; informing and updating local guidelines for empirical treatment of common infection syndromes; updating periprocedural or perioperative prophylaxis recommendations; providing a rationale for antimicrobial formulary selection; surveying local resistance and benchmarking; identifying targets for stewardship interventions and best practices; and providing the context for new drug susceptibility testing results. Unit specific (such as intensive care units) reporting may be helpful in targeting intervention strategies to improve antimicrobial usage and enhance infection prevention recommendations. The CLSI first published guidelines for the analysis and presentation of cumulative susceptibility test data in 2002, and updated them most recently in 2014 (127). The guidelines include 10 recommendations related to CASRs:

- » Analyze and present CASR at least annually.
- » Include only final, verified results.
- » Include only species with results for 30 isolates.
- » Include only diagnostic (not surveillance) isolates.
- » Eliminate duplicate isolates by including only first species' isolate/patient/period of analysis.
- » Include only routinely tested agents.
- » Report % susceptible (S) and exclude % (I) intermediate.

- » For *Streptococcus pneumoniae*, report data for both meningitis and non-meningitis breakpoints
- » For viridans group streptococci, report both % S and % I.
- » For *S. aureus*, report % S for all isolates and MRSA subset.

The clinical microbiologist is in an excellent position to understand how these recommendations influence the usefulness of reports, and to contribute to antimicrobial stewardship programs based on their expertise. Some institutions have also published CASRs online, which can be consulted on the web.

Table 1-5 provides a sample of a Cumulative Antimicrobial Susceptibility Report.

TABLE 1-5. RRUMC: ADULTS (<21 Y.O.) FIVE MOST COMMON GRAM-NEGATIVE BACTERIA- NON-URINE ISOLATES. % SUSCEPTIBLE																	
ORGAN SM	SOURCE	NO.ISOLATES	PENICILLINS			CEPHALOSPORINS				CARBAPENEMS			AMINOGLYCOSIDES			FLUORO-QUINOLONE	OTHER
			AMPICILLIN	AMPICILLIN-SULBACTAN	PIPERAZILLIN-TAZOBACTAN	CEFAZOLIN	CEFEPIME	CEFTAZIDINE	CEFTRIAZONE	ERTAPENEM	IMIPENEM	MEROPENEM	AMIKACIN	GENTAMICIN	TOBRAMYCIN	CIPROFLOXACIN	TRIMETHOPRIM/SULFAMETHOXAZOLE
<i>Enterobacter cloacae</i>	OP	81	R ¹	R	94	R	99	—	—	99	99	99	99	99	99	96	93
	IP	36	R	R	72	R	86	—	—	86	99	99	99	97	97	97	97
	ICU	58	R	R	60	R	72	—	—	86	99	99	99	95	91	95	86
<i>Escherichia coli</i>	OP	244	43	50	95	58	88	85	84	99	99	99	99	81	84	67	61
	IP	97	23	29	89	41	83	79	71	99	99	99	98	79	81	54	53
	ICU	93	19	22	73	30	70	69	66	96	98	98	97	72	70	43	50
<i>Klebsiella pneumoniae</i>	OP	99	R	82	95	78	91	92	90	96	96	96	97	92	91	88	82
	IP	62	R	63	84	63	89	91	83	94	94	94	94	89	90	89	86
	ICU	86	R	56	73	54	78	79	77	87	89	89	90	81	80	78	70
<i>Proteus mirabilis</i>	OP	68	75	90	99	9	99	99	94	99	25	99	99	90	96	69	75
	IP	21 ²	76	81	95	5	96	96	91	99	25	99	99	91	95	57	67
	ICU	18 ²	50	56	94	11	89	89	72	99	23	99	94	83	78	50	50
<i>Pseudomonas aeruginosa</i>	OP	299	R	R	90	R	92	94	R	R	87	91	92	88	95	81	R
	IP	91	R	R	69	R	84	74	R	R	73	79	97	89	92	71	R
	ICU	119	R	R	68	R	75	72	R	R	61	67	92	86	90	71	R

OP, outpatient (includes EMC); IP, inpatient (excludes ICU); ICU, intensive care unit.

¹ R = intrinsic resistance (inherent or innate antimicrobial resistance).

² Calculated from fewer than the standard recommendation of 30 isolates.

SOURCE: UCLA Health System. Available at: http://www.asp.mednet.ucla.edu/files/download/AMIC2015online?version_id=7520334.

Output indicators. Output indicators measure ASP deliverables, i.e., results that are attributable to the program itself. These are short term (< 5 years) indicators useful for monitoring progress at the national or institutional level





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Additional Resources

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