ANTIMICROBIAL STEWARDSHIP

A practical guide to implementation in hospitals

PIONEERING DIAGNOSTICS

INTRODUCTION

The objective of this booklet is to guide professionals and policy makers through the process of **developing and implementing a successful Antimicrobial Stewardship Program (ASP)** in their hospital, thereby improving the quality of both antibiotic prescribing and patient outcomes.

Throughout this booklet, we distinguish **3 building blocks of ASPs:**

- the **"Prerequisites"** (basic requirements);
- the **"What"** (appropriate antibiotic use practices);
- the **"How"** (improvement strategies).

Prerequisites must be in place to enable measurement to identify improvement targets. In addition, the prerequisites allow for the improvement of antibiotic use practices and consequently clinical outcomes of patients. Such a continuous cycle of measurement and improvement is fundamental to an ASP. In this booklet we will provide a **pragmatic step-wise approach to stewardship in daily practice**.

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Most of the recommendations in this booklet have been adapted from the IDSA guidelines[1,2], and from documents by the World Health Organization[3], US Centers for Disease Control and Prevention[4], the UK Health Security Agency[5,6], and the Dutch Masterclass on Antimicrobial Stewardship[7].

Since most research and evidence for Antimicrobial Stewardship (AMS) interventions continues to come from high income countries, the recommendations that are based on these studies need contextualization for low resource settings. In recent years, there has been an increasing number of studies and insights in hospital ASPs in settings with limited availability of resources[8]. Reviews summarizing interventions or identifying specific facilitators/barriers in these settings have been published[9-11].

We hope that this booklet will **inform, encourage and support healthcare professionals wishing to pursue hospital AMS initiatives** and thus combat antimicrobial resistance. We believe it will also contribute to the important task of **conducting hospital ASPs in tandem with stewardship in the community** and other settings, and furthermore to the fulfilment of the holistic objectives of the One Health approach including animal health and environment in comprehensively addressing antimicrobial resistance.

On behalf of the drive-AMS team, Antimicrobial Stewardship Program Radboudumc. Left-to-right: Jaap ten Oever, Neda Kostova, Karina van Lenthe, Marlies Hulscher, Teske Schoffelen, Robin Janssen, Jeroen Schouten. Not in the picture: Annelie Monnier, Nynke Jager, Heiman Wertheim.

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1

WHY PERFORM ANTIMICROBIAL STEWARDSHIP IN HOSPITALS?

The global burden of antimicrobial resistance (AMR) in 2019 was estimated to be 4.95 million deaths associated with bacterial AMR, including 1.27 million deaths attributable to bacterial AMR[12].

1.1 Antimicrobial resistance

THE RISING THREAT OF ANTIMICROBIAL RESISTANCE

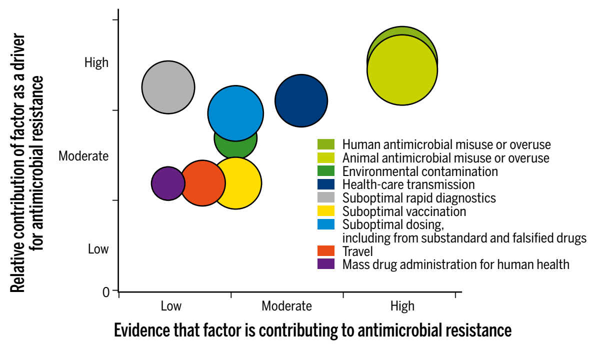
Antimicrobial resistance (AMR) has been identified as a **major threat to human health** by the World Health Organization (WHO) due to the lack of new antibiotics in the development pipeline and infections caused by multi-drug resistant pathogens becoming untreatable[13-15]. In 2015, the WHO set out the **Global Action Plan for AMR** and a subsequent broader stewardship framework[16].

COMBATING ANTIMICROBIAL RESISTANCE

There are numerous drivers for AMR **(Figure 1)**. Antimicrobial misuse and overuse in human health are key drivers, as are inappropriate use of diagnostics and a lack of infection prevention and control.

Figure 1. Mechanisms and drivers of antimicrobial resistance

Reproduced with permission from Holmes *et al. The Lancet* 2016;387:176-187[17]



To combat AMR, the WHO has released a people-centered core package of 13 interventions to guide national action plans on AMR[18].

As shown in Figure 2, a "four-pillar" approach is recommended and these pillars are supported by two foundational steps:

- effective governance, awareness and education;
- and strategic information through surveillance and research.

Figure 2. The WHO four-pillar approach

WHO core package of interventions to support national action plans. Geneva: World Health Organization; 2023[18]

PILLAR 1	PILLAR 2	PILLAR 3	PILLAR 4
PREVENTION OF INFECTIONS	ACCESS TO ESSENTIAL HEALTH SERVICES	TIMELY, ACCURATE DIAGNOSIS	APPROPRIATE, QUALITY-ASSURED TREATMENT

➔ **Antimicrobial stewardship (AMS)** is an important component of **pillar 4**, while **infection prevention and control (IPC)** is embedded in **pillar 1**. An integrated approach has been advocated, encompassing both AMS and IPC, which overlap in their goals, infrastructure, strategies and metrics[19]. AMS coupled with IPC measures have been shown to be more effective than AMS alone. Bauer *et al.*[20] reported a reduction of 66% in antibiotic resistance when combining AMS and IPC measures versus 19% for AMS alone.

➔ **Pillar 3** highlights that **good quality diagnostics are essential** to be able to fulfill the mission of AMS and IPC[21,22]. Any AMS or IPC program without diagnostics will be like sailing the oceans without a compass. Access to clinical microbiology is now also part of the essential diagnostics list of WHO[23].

1.2 Antimicrobial use

MISUSE AND OVERUSE OF ANTIBIOTICS

The last 80 years have witnessed the golden age of antibiotic discovery and their widespread use in hospital and community settings. Regarded as very effective, safe and relatively inexpensive, antibiotics have saved millions of lives. However, this has led to overuse and misuse in the human, animal and other sectors.

- **In US hospitals, antimicrobial use deviated from recommended practices for 55.9% of patients who received antibiotics for community-acquired pneumonia or urinary tract infection present at admission or who received fluoroquinolone or intravenous vancomycin treatment[24];**
- **20% of hospitalized patients experienced at least one antibiotic-associated adverse drug event when prescribed antibiotics[25].**

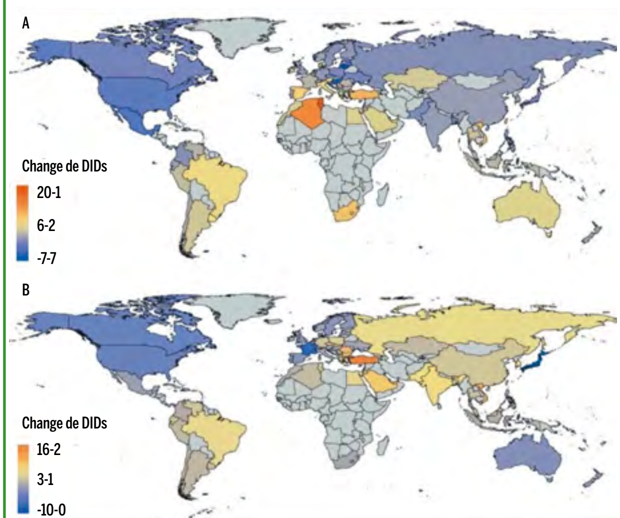
To help preserve the arsenal of effective antibiotics, the WHO has developed the Access, Watch, and Reserve (AWaRe) antibiotic classification system[26]:

- **Access** antibiotics are those that can treat a wide range of common pathogens and have lower resistance potential and should therefore be considered first-line options over antibiotics in the other categories;
- **Watch** antibiotics are those with higher resistance potential and those deemed "critically important antibiotics for human medicine";
- **Reserve** antibiotics should be used only for multidrug-resistant infections that cannot be treated by any other antibiotic.

Globally, the use of antibiotics in humans is accelerating, particularly in low resource settings **(Figure 3)**, as antibiotics become readily accessible and affordable, largely as a consequence of uncontrolled prescription, over-the-counter sales and self-medication with leftovers. The use of WHO **Watch** antibiotics increased 90% worldwide and 165% in low resource settings between 2000 and 2015[27]. However, the consumption of antibiotics is still higher in high- as compared to low-resource settings. Furthermore, the availability of essential **Access** antibiotics can be a particular problem in countries with limited resources[28,29].

Figure 3. Change in national consumption of Access (A) and Watch antibiotics (B), 2000–15, expressed in DIDs*

Reproduced with permission from Klein *et al. Lancet Inf Dis*. 2021;21(1):107-115[30]

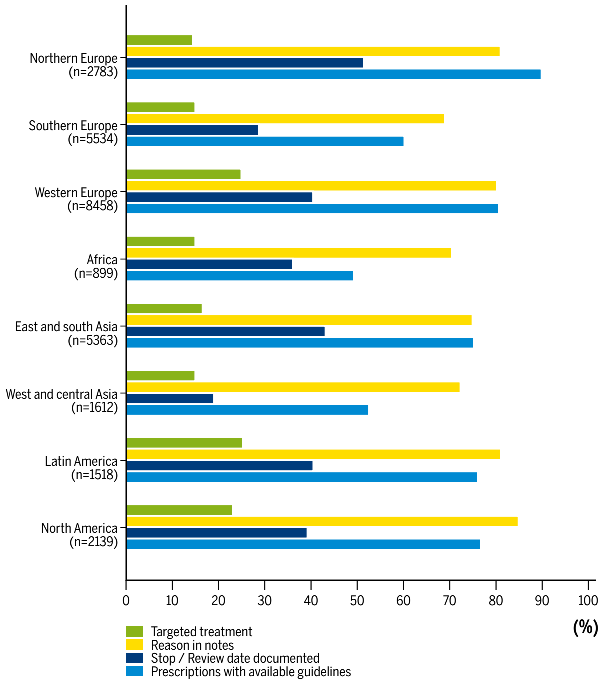


*DIDs=defined daily doses per 1000 inhabitants per day.

Global data on the quality of antimicrobial prescribing in hospitals from a global point prevalence survey [Global-PPS; https://www.global-pps.com] revealed significant variation in commonly used metrics of the quality of prescriptions **(Figure 4)**. Such real-world data provides much needed intelligence on what the problem most in need of improvement is, the scale of the problem and how to evalutate the effectiveness of AMS interventions.

Figure 4. Overview of antimicrobial/antibiotic quality indicators for adult inpatients by region, 2015 Global Point Prevalence Survey

Reproduced with permission from Versporten et *al. Lancet Global Health* 2018;6:619-629[31]



1.3 Antimicrobial stewardship

DEFINITION OF ANTIMICROBIAL STEWARDSHIP

Antimicrobial stewardship (AMS) can be defined as "A **coherent set of actions** which promote using antimicrobials in ways that ensure **sustainable access to effective therapy** for all who need them"[32]. This definition can be applied to actions at the individual (i.e., clinician) or institutional level, as well as the national and global level, and across human health, animal health and the environment[3].

Other definitions that help to understand AMS

➔ **as a description of activities**

"Antimicrobial stewardship is the effort to measure and improve how antibiotics are prescribed by clinicians and used by patients"[33].

➔ **as a description of goals**

"The primary goal of antimicrobial stewardship is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms, and the emergence of resistance"[1].

➔ **AMS can also simply be put as:**

"Prescribe the right antibiotic, at the right dose, by the right route, for the right duration, and at the right time".

Adapted from: www.cdc.gov/antibiotic-use/php/usaaw-partner-toolkit

THE ULTIMATE GOALS OF AMS (Box 1)

Box 1. The ultimate goals of AMS

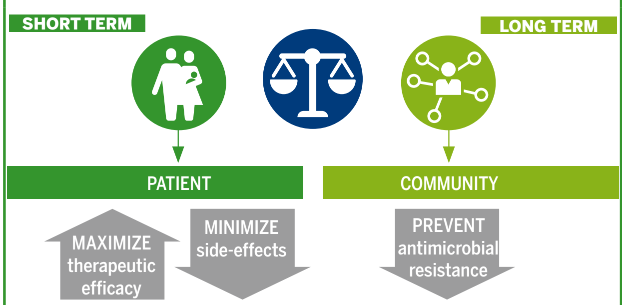
Adapted from Barlam *et al. Clin Infect Dis.* 2016;62:e51-7[2]

IMPROVE PATIENT OUTCOMES
REDUCE SIDE EFFECTS
PREVENT DEVELOPMENT OF RESISTANCE
PROMOTE COST-EFFECTIVE CARE

These goals cover both individual patients and the community, balancing both short- and long-term outcomes **(Figure 5)**.

Figure 5. The goals of antimicrobial stewardship for patient and community

Source: bioMérieux



DEFINITION OF ANTIMICROBIAL STEWARDSHIP PROGRAMS IN HOSPITALS

A hospital **Antimicrobial Stewardship Program (ASP)** is a coordinated hospital program that promotes compliance with the core principles of antimicrobial use by all prescribing healthcare professionals in the hospital.

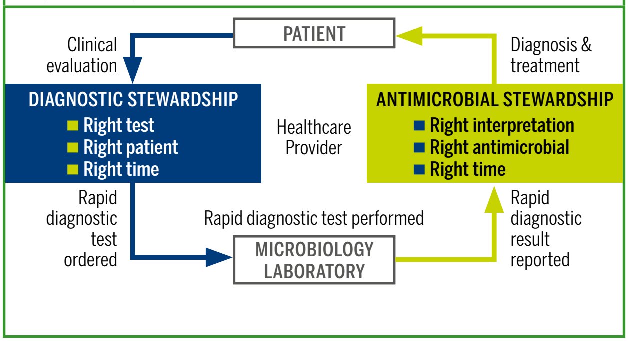
AMS AND DIAGNOSTIC STEWARDSHIP

"Diagnostic stewardship" is a term that has been increasingly used in the last decade, referring to the appropriate use of diagnostic laboratory testing to guide patient management. In this booklet we do not use the term "diagnostic stewardship"[34].

However, we do advocate for appropriate use of diagnostics as an essential part of any ASP **(Figure 6)**. Effective clinical microbiology is crucial for delivering high-quality healthcare.

Figure 6. Improving the diagnostic process as an inherent part of any ASP: Implementation of rapid molecular infectious disease diagnostics in the clinical setting

Reproduced with permission from Messacar et al. *J Clin Microbiol.* 2017;55:715-723[35]



1.4 Building blocks of an Antimicrobial Stewardship Program

International guidelines and policy statements include recommendations to guide the activities of the established AMS team[1,2]. These recommendations encompass two intrinsically different dimensions of stewardship: the "**What**" and the "**How**", which should be preceded by the "**Prerequisites**", which constitute **the base** of any ASP.

Therefore, the **three building blocks of an ASP** are:

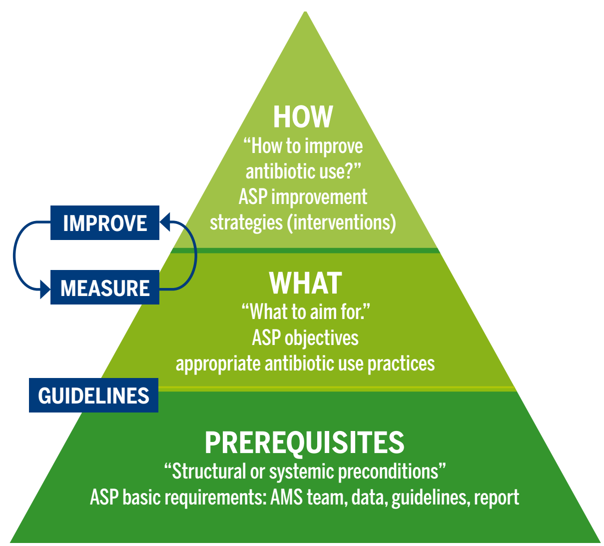
- **Prerequisites** for hospital efforts, i.e., the basic requirements of an ASP - refer to **structural or system requirements** that should be met to measure and improve antimicrobial use (see Chapter 2).
- The "**What**", i.e., what to aim for - refers to **key objectives or 'appropriate antibiotic use practices'** by professionals in patients. These key objectives constitute the focus of the ASP and are measured by the AMS team (see Chapter 3).
- The "**How**", i.e., how the AMS team will achieve these objectives - refers to **improvement strategies (i.e., interventions)** to be used by the AMS team to ensure that, in daily patient care, professionals actually use antibiotics appropriately (see Chapter 5). The "**How**" is essentially about **behavior change**.

The two core iterative activities of an ASP are to:

- **Measure** (appropriateness of) antibiotic use and resistance (see Chapter 4).
- **Improve** antibiotic use practices (see Chapter 6).

Figure 7. Schematic overview of the building blocks and core activities of an ASP

Adapted from De Waele et al. Intensive Care Med. 2016;42:2063-2065; Hulscher *et al. Clin Infect Microbiol*. 2017;23:799-805; Kallen et al. *J Antimicrob Chemother*. 2018;73:3496-3504[36-38]



PREREQUISITES OF AN ANTIMICROBIAL STEWARDSHIP PROGRAM

Although ASPs depend on local needs and issues, as well as available expertise and other resources, there are a number of PREREQUISITES to be met to enable a good stewardship program.

2.1 Human resources and collaboration

CREATE AN AMS TEAM

An AMS team should be established that is responsible for the daily management of the hospital ASP.

➔ **The main tasks of the AMS team can be summarized as follows:**

- Ensure that the **prerequisites for ASP** are met (this Chapter);
- Coordinate the **daily monitoring and advice** for specific antimicrobial prescriptions and specific patient categories (e.g., with *S. aureus* bacteriemia) (see Chapter 5);
- Systematically **measure and improve** the appropriateness of antibiotic use (see Chapters 4 and 6).

Core members of a multidisciplinary AMS team include:

- Infectious disease physician;
- Clinical pharmacist with infectious disease training;
- Clinical microbiologist.

The training, functions and tasks of these specialties may differ from country to country. The AMS team must have the **mandate** from the Executive Board (i.e., the governing body or management of the hospital) and must have **expertise** (both in infectious disease and change management), **credibility** and **leadership qualities**. The choice of who leads the AMS team depends on locally available expertise and the role of different specialties in the respective hospital setting.

Other AMS team members recommended to be included:

- Specialized nurse;
- Infection control officer (nurse or medical specialist);
- Hospital epidemiologist;
- Professional with experience in the field of quality of care / implementation scientist / behavioral scientist;
- Information system specialist.

The value of specialized nurses in AMS teams

Participation of **AMS-trained nurses** in AMS teams is of particular value. They can fulfil an important role in the **monitoring and evaluation of antibiotic use**[39]. Nurses could also have an important role in multidisciplinary meetings. In addition, they may monitor whether professional advice, issued by the AMS team, is adhered to. Moreover, nurses may have an important part in education and raising awareness related to AMS and AMR. By visiting the various departments, accompanied or not by another member of the AMS team, nurses have the potential to help increase the visibility and recognition of the AMS team at the hospital. In resource-limited settings, nurses are often in the frontline of antibiotic prescription.

SECURE SUPPORT, BUDGET AND COLLABORATION

Support

The **endorsement of the hospital Executive Board**, as well as the acceptance and support of hospital's medical specialties, is essential for the success of an ASP. Creating a sense of urgency in the Executive Board around the need to contain AMR and the importance of AMS, is therefore the first task of the AMS team **(Box 2).**

The Executive Board of the hospital should **formally appoint and mandate an AMS team** to enable the AMS team to perform its duties. The AMS team must embed the ASP in the local structure of the hospital, e.g. within the hospital's quality improvement and patient safety governance structure. In addition, the AMS team should engage representatives from all medical specialities in the hospital to ensure support for the ASP.

Box 2. Sharing data is instrumental to create a sense of urgency at the Executive Board level to support the ASP

Source: bioMérieux

- High levels of antimicrobial consumption (e.g., carbapenems compared to international standards);
- High resistance rates (e.g., carbapenem-resistant Enterobacterales);
- Poor patient outcomes (e.g., high rates of surgical site- or *Clostridioides difficile* infections);
- Mandate to implement a stewardship program (e.g., driven by local health regulators or other similar organizations having such a program in place).

Budget

The **Executive Board of the hospital should provide a budget** to enable the AMS team to perform its duties. For that reason, the AMS team should make a case for the need for human resources dedicated to AMS activities, and appropriately calculate the resources needed. This calculation should consider which AMS team activities will be undertaken (by whom, and how often) and take into account the size of the hospital. Based on this, a rough estimate can be made of the number of hours required of each of the parties involved[40-43].

Collaboration

It is critical that the **AMS team collaborates with other groups**, including the hospital committee responsible for hygiene and infection prevention, and the local antibiotic guideline committee. Creating joint committee meetings can be considered. During these joint meetings, the AMS team can report on its activities, local resistance data and the quantity and quality of antibiotic use can be shared and discussed, and the goals of the AMS team for the next 6 to 12 months can be established.

2.2 Availability of guidelines and antibiotic formulary

CREATE A LOCAL INFECTION-SPECIFIC TREATMENT GUIDELINE

This is an essential prerequisite for the performance of an ASP which **provides treatment advice for common infections** such as community-acquired pneumonia and urinary tract infection. The guideline not only provides guidance for the treating practitioner, it also serves within the ASP **as a normative framework** for the AMS team to assess the quality of antibiotic use within the hospital. It should provide explicit criteria for the "**appropriateness of use**", so that unjustified use can be determined.

➔ The recommendations on empirical and targeted treatment in local infection-specific treatment guidelines should be based on (inter) national clinical practice guidelines, and take into account local resistance patterns when available.

CREATE A LOCAL ANTIBIOTIC FORMULARY

It is helpful for the AMS team to have a local antibiotic formulary that lists the **available antibiotics in the local setting**. This list can be extracted from a hospital drug formulary.

➔ The antibiotics mentioned in the local infection-specific treatment guideline should be part of the antibiotic formulary.

MAKE A LIST OF RESTRICTED-USE AND OTHER LIMITED-INDICATION ANTIBIOTICS, TAILORED TO THE LOCAL SITUATION.

Together with stakeholders, such as the local antibiotic guideline committee and/or the relevant medical specialties, the AMS team should **determine which antibiotics are classified for restricted use only** and require monitoring by the AMS team. These drugs are allowed to be prescribed only in cases of an actual or suspected infection with a microorganism that is not susceptible to the common antibiotics.

➔ The WHO AWaRe classification of antibiotics may be used as the base for the restricted use list (www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.04).

2.3 Access to data and means to process data

COLLECT DATA ON QUANTITY AND QUALITY OF ANTIBIOTIC USE

The AMS team should be enabled to collect data on antibiotic use and process these raw data into quantity metrics. The **hospital pharmacy can facilitate access to data** on the volume of antibiotic use and help convert these data into meaningful antibiotic utilisation rates (expressed in antimicrobial consumption metrics such as defined daily dose (DDD) and days of therapy (DOT).

➔ To collect data on quality of antibiotic use, **point prevalence surveys (PPS)** and **audits** should be carried out by the AMS team (see Chapter 4).

OBTAIN DATA ON LOCAL, REGIONAL AND NATIONAL ANTIMICROBIAL RESISTANCE

Knowledge of local resistance data is important for performing an ASP, for example, to identify emerging resistant microorganisms and pathogens – locally, regionally or nationally. Such local monitoring takes place in close collaboration with the clinical microbiology laboratory and the IPC department.

➔ Having a **well-functioning clinical microbiology laboratory** in place with sufficient capacity and capability is therefore of the utmost importance for a successful ASP.

SET UP INFORMATION TECHNOLOGY (IT) SUPPORT

Set up **IT support** and include it in the ASP budget. Support of an IT specialist plays an important role in facilitating:

1. Daily monitoring of prescriptions;
2. Measuring the quality of use;
3. Reporting data in a meaningful way.

The AMS team should decide with data providers about which data should be reported, at what frequency and how it should be displayed. Depending on the availability of advanced electronic patient files, relevant data may be extracted from these files and operationalized into meaningful metrics (Quality Indicators, see Chapter 4).

➔ In settings where electronic patient files are not available, AMS teams should find support and budget to collect data manually.

ENSURE LEGAL ARRANGEMENTS FOR ACCESSING AND PROCESSING MEDICAL DATA

The tasks and objectives of the AMS team **are explicitly aimed at improving the quality of care**. To fulfil these tasks, the AMS team needs to obtain relevant data from patient files via the various hospital information systems.

➔ The AMS team should be **authorized to access and process medical data** despite absence of a direct treatment relationship between the corresponding patients and the members of the AMS team. Country-specific regulations on this matter should be complied with.

2.4 Policy and reporting

MAKE A POLICY PLAN

After the AMS team is installed and financial support is secured, a policy plan or action plan should be defined. This plan needs to be **regularly evaluated** and adjusted in case of modifications – at least once a year. It should cover the following topics:

- Organisational structure;
- Area of attention;
- Task coordination;
- The baseline situation;
- Short-term policy plan;
- Distribution of tasks;
- Meeting frequency;
- The data plan.

REPORT ANNUALLY

At least once a year the **AMS team should prepare a report**. In addition to the previously mentioned elements of the policy plan, this report should ideally contain information related to:

- The stewardship activities performed;
- The status of local antibiotic resistance and its trends;
- Information on the quantity of antibiotic use, including the restricted use antibiotics, ideally stratified per department;
- Information on the quality of antibiotic use (split per department), e.g. based on data from point prevalence surveys;
- The results of supplementary measurements of antibiotic use and improvement projects mentioned in the annual action plan.

➔ This annual report should be presented to the Executive Board and other stakeholders such as medical specialties, the local antibiotic committee and the hospital committee responsible for hygiene and infection prevention.

2.5 Checklists with prerequisites

The prerequisites as described above, can also be found in the CDC's **The Core Elements of Hospital Antibiotic Stewardship Programs**. This document, which was updated in 2019[4], identifies key structural and functional aspects of effective ASPs. (N.B. In this document, however, prerequisites are mixed and overlap with ASP objectives and improvement strategies.)

Another list of core elements and checklist describing **essential and minimum standards for ASPs in hospitals** worldwide is also worthy of review for prerequisites of such programs **(Figure 8)**.

Initiating ASPs in hospitals in **resource-limited settings** involves more challenges than in high-income settings[8]. Often the prerequisites are not yet in place and need to be addressed first, while sometimes the hospital system allows ASP integration in current practices[45].

In addition, factors related to healthcare facilities, e.g., lack of basic infrastructure and equipment, large patient numbers and shortage of healthcare personnel with high turnover can add to the challenge of starting an ASP in resource-limited settings.

➔ A practical toolkit that includes advice with regard **to prerequisites in low resource settings** is available from the WHO[3].

Figure 8. Core elements and checklist items for global hospital AMS programs

Adapted from Pulcini *et al. Clin Microbiol Infect.* 2019;25:20-25[44]

CORE ELEMENT 1

Senior hospital management leadership towards antimicrobial stewardship

This section relates to governance of the programme by hospital executives, and specifies how senior hospital management supports the antimicrobial stewardship programme

CORE ELEMENT 2

Accountability and responsibilities

CORE ELEMENT 3

Available expertise on infection management

CORE ELEMENT 4

Education and practical training

CORE ELEMENT 5

Other actions aiming at responsible antimicrobial use

CORE ELEMENT 6

Monitoring and surveillance (on a continuous basis)

Does your hospital monitor the quality of antimicrobial use at the unit and/or hospital wide level?

This can be done for example by undertaking point prevalence surveys or audits, assessing appropriateness of infection management and antimicrobial prescription (e.g. indication, choice and duration of antibiotic therapy in pneumonia or surgical prophylaxis according to policy/guidance)

CORE ELEMENT 7

Reporting and feedback (on a continuous basis)

All these reports should also be shared with the hospital management leadership

THE "WHAT" OF AN ANTIMICROBIAL STEWARDSHIP PROGRAM

The "WHAT" of AMS refers to objectives that describe appropriate antibiotic use practices to be performed by healthcare professionals in individual patients regarding indication, choice of drug, dose, route, duration or de-escalation of treatment.

3.1 Generic AMS objectives

Generic AMS objectives refer to objectives describing appropriate antibiotic use practices in the treatment of **bacterial infections in hospitalized adult patients (Table 1)**. These objectives can serve as a list of improvement targets of the AMS team.

Table 1. Examples of generic hospital AMS objectives

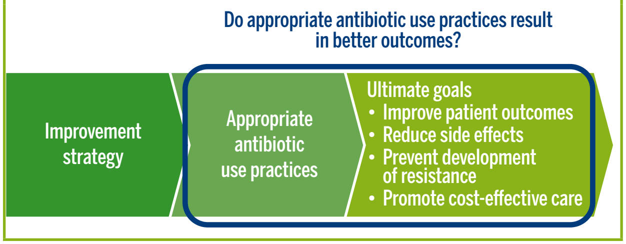
Adapted from Van den Bosch *et al. Clin Infect Dis.* 2015;16:281-291[46]; Kallen *et al. Infect Dis Rep.* 2017;9:6821[47]; Monnier *et al. J Antimicrob Chemother.* 2018;73:vi30-vi39[48]

AMS OBJECTIVE	DEFINITION
Empirical therapy according to the guidelines	Prescribe empirical systemic antibiotic therapy according to local guide or national guidelines
Obtain blood cultures	Take at least two sets of blood cultures before starting systemic antibiotic therapy when bacteremia is suspected
Obtain cultures from the site of infection	Take cultures from suspected sites of infection, preferably before starting systemic antibiotic therapy
De-escalation of therapy	Change to narrow-spectrum antibiotic as soon as culture results of the causative pathogen are available
Adjustment of therapy to renal function	Adjust dose and dosing interval of systemic antibiotics to renal function
Switch from intravenous to oral therapy	Switch after 48-72 h, when the clinical condition of the patient is stable, oral intake and gastrointestinal absorption are adequate, and when sufficiently high concentrations in blood with a suitable oral antibiotic can be achieved
Documented antibiotic plan	Should be included in the case notes at the start of systemic antibiotic treatment and should include indication, drug name and dose, and administration route and interval
Therapeutic drug monitoring	Perform for antimicrobials with a narrow therapeutic spectrum and an increased risk of toxicity (such as gentamicin and vancomycin) according to guidelines
Discontinuation of antibiotic therapy if infection is not confirmed	Discontinue empirical treatment based on lack of clinical or microbiological evidence of infection
Duration of antibiotic therapy	Stop antibiotic treatment according to local or national guidelines

These generic hospital AMS objectives describing appropriate antibiotic use practices should be based on evidence related to ultimate AMS goals **(Figure 9)**.

Figure 9. Does stewardship work: the evidence base of the 'What' of AMS

Reproduced with permission from Hulscher *et al. Clin Infect Microbiol.* 2017;23:799-805[37]



A systematic review[49] showed abundant but low quality evidence that several of these generic AMS objectives can help achieve the ultimate AMS goals. For example, meta-analysis of studies on the objective "empirical choice of antibiotic according to the local guideline" showed a 35% relative risk reduction for mortality.

In the UK, generic AMS objectives of stewardship have been adapted into a **pragmatic approach ("Start Smart, Then Focus")** that is aligned with the clinicians' daily decision-making process **(Figure 10)**.

3.2 Specific AMS objectives

AMS objectives for appropriate antibiotic use practices in the treatment of **specific bacterial infections in hospitalized patients** can be found in infection-specific treatment guidelines. These guidelines are important references to define appropriate patient care, reflecting the current state of knowledge and providing recommendations for clinical practice.

The Infectious Diseases Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) are professional societies that develop guidelines for various infectious diseases [available from https://www.idsociety.org/practice-guideline/practice-guidelines and https://www.escmid.org/escmid-publications].

Also, the National Institute for Health and Care Excellence (NICE) offers infection-specific antimicrobial prescribing guidelines [available from https://www.nice.org.uk/guidance].

The WHO has recently published the AWaRe antibiotic book that provides evidence-based guidance for the most common clinical infections in both hospital settings and primary care[26].

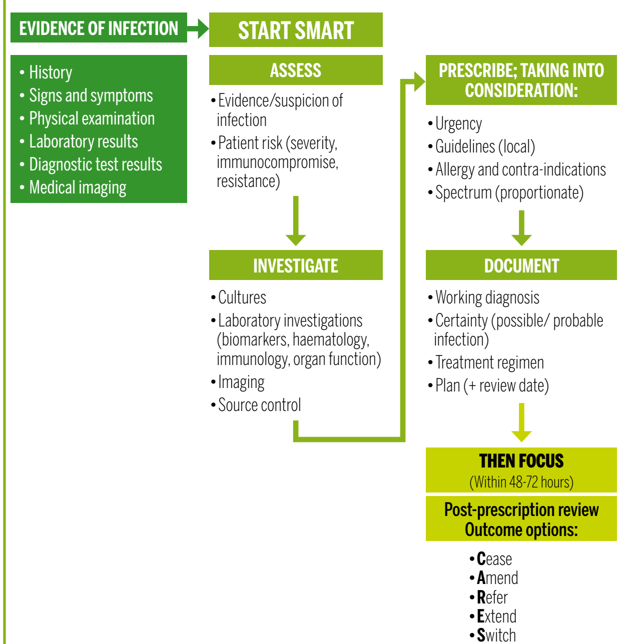
When recommendations from (inter)national guidelines are translated into local hospital guidelines, it is important that the **local antimicrobial resistance patterns** are taken into account[50].

3.3 Prioritizing AMS objectives

With limited time and resources, AMS teams should select AMS objectives that most need their attention, pragmatically prioritizing those most relevant to the local setting, taking into account the available and changing evidence. Initial focus could be on objectives where the **greatest benefit is expected**, based on measurement of current practices (see Chapter 4). Successful achievements in the beginning are very important for AMS teams in order to maintain and increase support. Therefore, it is advisable to initially focus on objectives where chances for success are higher (e.g., because the necessary prerequisites are met).

Figure 10. Antimicrobial stewardship treatment algorithm

Adapted from Start Smart Then Focus: Guidance for Antimicrobial Stewardship in hospitals (PHE, UK)[5]



4

MEASURING ANTIBIOTIC USE AND RESISTANCE

MEASURING is an essential activity of every ASP.

Routinely collected data on antimicrobial use and antimicrobial resistance patterns is often a starting point for improvement strategies.

Deciding what to measure, how often to measure and how to communicate and act upon the data, depending on available resources and time, is key.

4.1 Measuring antibiotic use

> "If you cannot measure it, you cannot improve it"
> Lord Kelvin 1824-1907

4.1.1 Quantity of antibiotic use

Quantity measures or metrics reflect the **volume or costs of antibiotic use**. Fair comparison of antibiotic use is only possible through **standardization** (see page 28: **Denominator**). It is recommended that the quantity of antibiotic use should be expressed in at least two metrics simultaneously[51,52]. Different units of measurement can be used for both the numerator and the denominator of quantity metrics, namely:

Numerator

- **Defined Daily Dose (DDD)**: Represents the average daily maintenance dose of an antimicrobial for its main indication in adults [WHO Collaborating Centre for Drug Statistics Methodology: https://www.whocc.no/]. For instance, the DDD of oral amoxicillin is 1500 mg, so a patient receiving 500 mg every 8 hours for 5 days consumes 5 DDDs.
- **Days of Therapy (DOT)**: One DOT represents the administration of a single antibiotic on a specific day regardless of the number of administered doses or dose strength, and is mostly based on prescription data at the patient level (recommended method in IDSA guidelines; CDC preferred metric). This is why DOT is not influenced by dose adjustments (such as in children or renal failure), in contrast to DDD.
- **Length of Therapy (LOT)**: Number of days a patient receives systemic antimicrobial agents, irrespective of the number of different drugs.

All antibiotic prescriptions can be expressed in DDD, DOT and LOT (see example on the next page).

EXAMPLE

A patient is hospitalized for moderate-severe CAP and treated with amoxicillin (3 x 1 g PO, 7 days) + azithromycin (1x 500 mg PO, 5 days), following local guidelines.

DDD:	DOT:	LOT:
14 + 8.3 = **22.3**	7 + 5 = **12 days**	**7 days**

Denominator

Usage data may then be divided by a **measure of hospital activity**, such as number of admissions or in-patient bed days, to provide more meaningful trend analysis and comparison.

In-patient bed days is more commonly used as these data can be more easily obtained than admissions data. Other denominators are also used and their strengths and limitations have been described[51,53,54].

Quantity measures

DDDs or DOTs per 100(0) patient-days are frequently used to measure the quantity of antibiotic use in hospitals[51,52].

A simple way to initiate further analysis of the consumption data is to look at the proportion of DDDs in AWaRe groups or any other relevant clinical categories.

Alternatively, antibiotic spectrum could be incorporated in the analysis of the consumption data[55]. The **Antibiotic Spectrum Index (ASI)** is an example of a quantity metric that reflects the spectrum of the antibiotic prescriptions[56].

Hospital level data may be transferred to a national database for further analysis and benchmarking [for example: NethMap 2023 report, available from: https://swab.nl/nl/exec/file/download/266]

4.1.2 Methods for measuring quantity of antibiotic use

Relevant sources for information on quantity of antibiotic use:

- **Prescription data at individual patient level**, using an electronic prescribing system through the electronic patient file if available. These data can be used to calculate DOT.
- **Data from hospital pharmacy (electronic) systems**, showing antibiotics delivered to each ward (dispensing data) and used as a proxy measure for antibiotics administered to patients. These data can be used to calculate DDD.

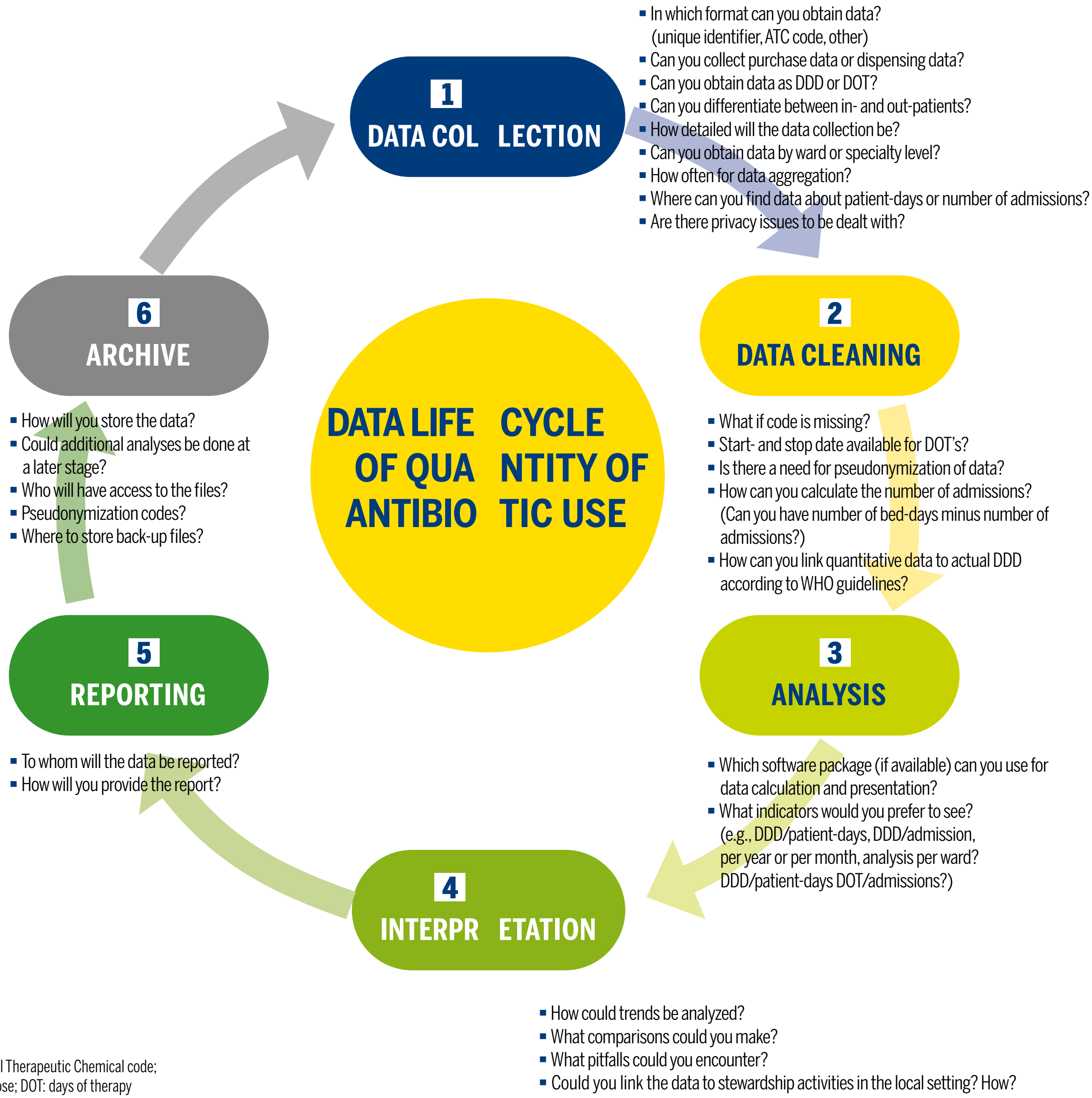
A clear understanding of the data sources (prescription data at the patient level or aggregated dispensing data per department) and a uniform approach to data registration and data extraction procedures are very important to obtain reliable measurements. Discrepancies in the use of data sources and data registration or extraction can affect the outcome of the calculation, and must be taken into account for the interpretation[57].

The Antimicrobial Consumption (AMC) Tool is a simple computer tool to **measure antibiotic consumption** in hospitals and hospital wards. It transforms aggregated data provided by hospital pharmacies (generally as a number of packages or vials) into meaningful antibiotic utilization rates. [AMC Tool, available from: http://amu-tools.org]

A **step-by-step model** for data collection, analysis and reporting is shown in **Figure 11**.

Figure 11. Data life cycle of quantity of antibiotic use

Property of The Working Group Surveillance of Antibiotic Use of the Dutch Working Party on Antibiotic Policy[58]; reproduced with permission.



ATC code: Anatomical Therapeutic Chemical code;
DDD: defined daily dose; DOT: days of therapy

4.1.3 Quality of antibiotic use

Quantity measures of antibiotic use provide limited insight into which antibiotic use practices need improvement. **Measurement of the quality of antibiotic use** is essential to identify antibiotic use practices in need of improvement and to evaluate the impact of stewardship interventions on clinical practice. **Quality Indicators (QIs)** have been developed to define appropriate antibiotic use.

> **Quality of care can be measured using QIs. These are defined as "measurable elements of practice performance for which there is evidence or consensus that they can be used to assess quality, and hence change in the quality of care provided"[59]**

QIs should preferably be **easy to measure (feasible)** and provide **reproducible results (reliable)** through the use of strictly described decision rules for extracting data and calculating QI scores.

There are three types of QIs **(Figure 12)**:

- **Structure QIs** - reflect the organization at the hospital or ward level; they indicate whether a particular facility or structure, considered a prerequisite for providing appropriate care, is in place. They are typically expressed as a dichotomous variable.

  For example: an AMS team - consisting of at least an infectious disease physician, a clinical pharmacist with infectious disease training and a clinical microbiologist - should be appointed in the hospital.

- **Process QIs** - aim to evaluate whether the actual care delivered is appropriate. They are typically expressed as the percentage of eligible patients who received the recommended care.

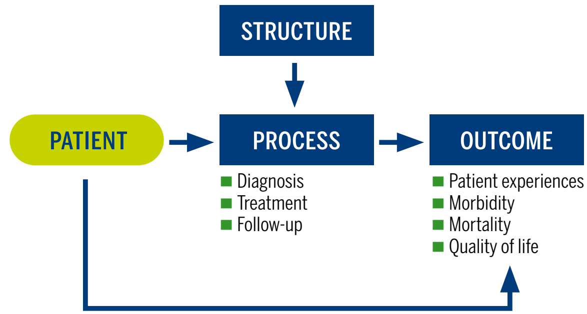
  For example: empirical antibiotics should be changed to pathogen-directed therapy when culture results become available.

- **Outcome QIs** - focus on the outcomes or results of the care delivered and are typically expressed as the percentage of patients with the (un)desired outcome.

  For example: mortality and re-admission.

Figure 12. Three types of quality indicators and their interrelation

Adapted from Donabedian. *JAMA*. 1988;260:1743-1748[60]



Balancing outcome QIs

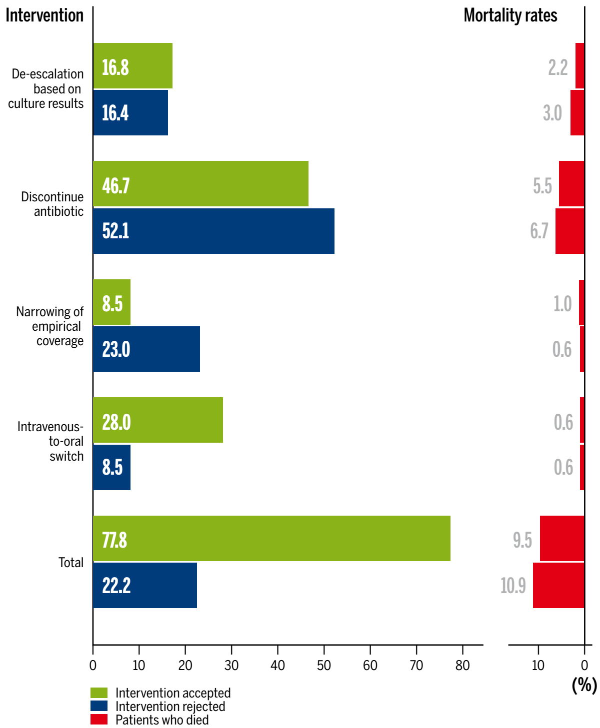
In most situations, AMS improvement interventions (see Chapter 5) aim to reduce unnecessary antimicrobial exposure (e.g., choice of narrower spectrum, or shorter duration) and improve quality of prescribing while preserving clinical outcome. When the improvement intervention is targeted toward certain classes of antibiotics, the AMS team should be aware that it may lead **to compensatory consumption of alternative antibiotics** ("squeezing the balloon" phenomenon[61]), which may also entail even worse consequences on bacterial resistance.

Moreover, there is often some degree of **real or perceived risk of patient-level harm** specific to the improvement strategy, patient population, setting and disease, which could prevent adoption of the intervention - even if it were effective in reducing antimicrobial exposure[62]. The AMS team should bear this in mind and consider collecting data that shows no adverse impact on clinical outcome, in order to reassure **and engage medical teams and hospital management**.

> **For example:** a Singapore-based study **(Figure 13)** showed that in patients whose physicians accepted suggested ASP interventions, there was shorter duration of hospital stay, reduction in 14-day re-infection rates and overall no difference in all-cause mortality (all: balancing measures).

Figure 13. Interventions aiming for appropriate antibiotic use practices that may impact morbidity and mortality

Reproduced with permission from Liew YX *et al. Int J Antimicrob Agents* 2012;40:55-60[63]



Operationalizing QIs

Preferably, **AMS teams should use existing QIs** that have been systematically extracted from international guidelines and the literature[64-67].

If no QIs exist for the antibiotic use aspect that the AMS team is interested in, a **systematic consensus procedure** may be followed to develop evidence and expert-opinion based QIs[68].

Practical guidance on how an AMS team can use (i.e., operationalize) QIs to measure the quality of antibiotic use in their hospital and **identify targets for improvement** is provided by Stemkens *et al. Clin Microbiol Infect* 2023[69] **(Table 2)**.

Table 2. Step-by-step guidance on how AMS teams can use QIs to measure the quality of antibiotic use*

Adapted from Stemkens *et al. Clin Microbiol Infect.* 2023;29:182-187[69]
*Refer to the publication for a more detailed description of this guidance.

Step 1	Select a topic and a patient population of interest *E.g.: AMS teams may receive signals from within their organization that a problem exists in the current delivery of care. Sometimes, new evidence from a recent trial or a guideline update becomes available.*
Step 2	Select a set of QIs to assess the quality of antibiotic use *Numerous sets of QIs for antimicrobial use have been developed for various infectious diseases.*
Step 3	Prioritize the QIs and select those to be measured *AMS teams should focus on 3-5 QIs where the greatest benefit is expected.*
Step 4	Operationalize the QIs *All data elements that form a QI must be clearly defined to make them measurable.*
Step 5	Develop a scoring algorithm for quality indicators *To calculate the QI performance score, the number of eligible patients with the recommended care or outcome (numerator) is divided by the total number of eligible patients (denominator), multiplied by 100.*
Step 6	Select the data collection method and create a database *Only well-documented variables can be retrieved retrospectively without risk of bias. If not feasible, data collection should be performed prospectively.*
Step 7	Develop locally tailored procedures for standardized data collection *A clear and coherent measurement plan should be established to ensure uniform and objective data collection.*
Step 8	Collect the data *A sufficiently large sample size is critical to ensure that the results obtained are an accurate estimate of the QI performance score for the entire population.*
Step 9	Analyze the results *QI performance score is the primary parameter that represents quality of care. Validity should be assessed by measuring so-called clinimetric properties (applicability, measurability, room for improvement and inter-observer reliability).*
Step 10	Select targets for improvements *The QI measurement results offer guidance to AMS teams for developing a strategy to improve quality of care. QIs should be remeasured to evaluate the effect of the intervention.*

4.1.4 Methods for measuring quality of antibiotic use

Point prevalence surveys (PPS) and audits are important stewardship tools to measure quality (i.e., appropriateness) of antibiotic use.

Point prevalence survey

A PPS is a **cross-sectional measurement** ("snapshot") of antimicrobial use within a unit or hospital. It is carried out at **one single moment in time**, collecting information from patients on antimicrobial therapy on that specific day, including:

- Demographic information (e.g., age, sex)
- Lab-related information (e.g., cultures sent to lab; treatment based on biomarker?)
- Information on the antimicrobial prescription, including:
  - Antimicrobial name, dose, route, frequency
  - Treatment targeted or empirical?
  - Indication for treatment (e.g. community-acquired, healthcare-associated, prophylaxis)
  - Diagnosis (e.g. pneumonia, orthopaedic surgical prophylaxis....)
  - Reason for treatment documented?
  - Choice of antibiotic guideline-compliant?
  - Stop/review date documented?

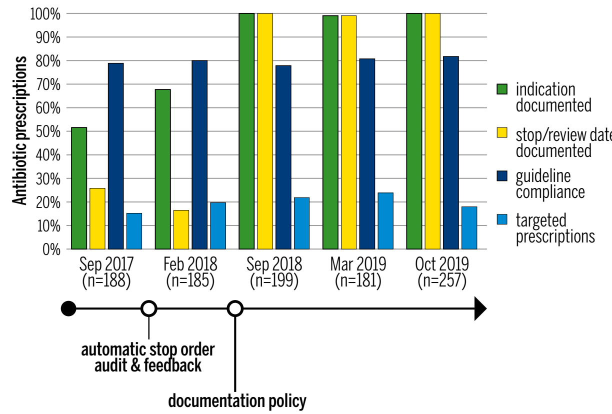
PPSs can be used to:

- **Establish baseline prescribing information** and identify potential areas for quality improvement, by gaining insight into hospital antimicrobial prescribing patterns.
- **Evaluate the effect of antimicrobial stewardship** from repeated activities over time by describing QI scores by PPS measurements **(Figure 14)**.
- **Create awareness** on appropriate antimicrobial prescribing by communicating PPS results to everyone involved (clinicians, pharmacists, nurses, management etc.).

The PPS method, while effective for assessing antibiotic use at one specific moment, may not provide comprehensive insights for less common indications or rarely prescribed antibiotics. In addition, some stewardship objectives, such as duration according to guidelines and IV-oral switch therapy, can only be evaluated in part or not at all through PPS.

Figure 14. Evolution of hospital performance for QIs assessing appropriate antibiotic prescribing for therapeutic use, shown by repeated Global-PPS measurements

Reproduced with permission from De Guzman Betito *et al. J Glob Antimicrob Resist.* 2021;26:157-165[70]



AMS teams may choose to design their own PPS method, or can use existing PPS methods and protocols.

An **e-learning module** is available to train those undertaking these surveys [https://www.futurelearn.com/courses/point-prevalence-surveys]. Existing PPS methods are offered for example by **Global-PPS** [https://www.global-pps.com], **WHO-PPS** [https://www.who.int/publications/i/item/WHO-EMP-IAU-2018.01] or **ECDC** [https://www.ecdc.europa.eu/sites/default/files/documents/PPS-HAI-AMR-protocol.pdf].

Audits

Audits are small-scale and detailed measurements of **specific antibiotic use practices** from patient records to assess the appropriateness of antibiotic use over an extended period by comparing them to AMS objectives. These can further enhance data collected through PPS. Audits enable a more focused and representative examination of the quality of antibiotic use in certain departments, certain patient categories or of certain stewardship objectives that cannot be measured by PPS.

4.1.5 Proxy indicators

Measuring quantity metrics is time-efficient, but provides limited insight into which antibiotic use practices need improvement. Measuring QIs takes effort and time, but identifies improvement targets. **Proxy indicators** are midway between quantity metrics and QIs. These novel indicators can be constructed from easily available quantitative data that, with some adjustment, provide the approximate quality of antibiotic use. In contrast to QIs that accurately reflect the appropriateness of each antibiotic prescription, proxy indicators can only strongly suggest that antibiotic use at an aggregated level (not the prescription level) is appropriate or not, depending on whether the set target is met or not[71,72].

> **For example**: Seasonal variation of total antibiotic use can be calculated as a proxy indicator since overprescription in the winter might possibly be the result of unnecessary antibiotic use for viral infections.

4.2 Surveillance of antimicrobial resistance

Local resistance data may be obtained from the microbiology laboratory, ideally through electronic systems if available, and reported systematically and regularly in a **cumulative antibiotic susceptibility report**. A special focus should be on **highly resistant micro-organisms**. Local resistance data allows monitoring of trends overtime, and can be observed to identify targets for improvement interventions.

In resource-limited settings, surveillance of AMR is often particularly challenging. The availability of clinical microbiology laboratories is limited, even in hospitals, leading to paucity of diagnostics and representative surveillance data[29]. There is a bias towards resistance in these settings as often microbiology is done only in cases of treatment failure **(Table 3)**.

The **challenges of implementation** of clinical bacteriology in low-resource settings and **a framework** as to how these difficulties could be overcome is provided by Ombelet *et al*[73].

Table 3. Influence of culture rate on resistance proportions and resistance rates

Reproduced from De Kraker *et al. PLoS Med.* 2016;13(11):e1002184[74] CC BY 4.0

Culture rate	Proportion: Resistant isolates/total isolates	Incidence: Resistant isolates/patient-days
High	Too low	"True"
Adequate	"True"	"True"
Low (still detecting all resistant isolates)	Too high	"True"
Very low (not detecting all resistant isolates)	Very high	Too low

Hospital-level data may be transferred to national databases for further analysis. Surveillance data of AMR at a higher level (regional, global) are used to evaluate regional and global trends, e.g.:

- **CDC**: National Antimicrobial Resistance Monitoring System [https://www.cdc.gov/narms/]
- **ECDC**: consolidation of resistance data at the European level [EARS-Net] with consolidation of antibiotic use [ESAC-Net]
- **WHO**: Global Antimicrobial Resistance and Use Surveillance System [GLASS; available from https://www.who.int/initiatives/glass]

THE “HOW” OF AN ANTIMICROBIAL STEWARDSHIP PROGRAM

The “HOW” of AMS refers to improvement strategies to ensure that, in daily patient care, professionals use antibiotics correctly (“how to improve antibiotic use?”). These are essentially strategies aimed at changing professional behavior.

5.1 AMS improvement strategies

There are many strategies to improve antibiotic use in hospitals, which can be applied on an (inter)national, institutional and/or individual level[75]. Hospital AMS teams focus mainly on **interventions at institutional or individual level**, indirectly or directly targeting healthcare professionals **(Table 4)**.

Table 4. Examples of improvement strategies to bring about change in the behavior of healthcare professionals

Reproduced with permission from Hulscher *et al. Lancet Infect Dis,* 2010;10:167-175[75], based on Effective Practice and Organisation of Care (EPOC). EPOC Taxonomy; 2015

PERSUASIVE STRATEGIES TO IMPROVE ANTIMICROBIAL PRESCRIBING	
Distribute educational materials (guidelines, etc.)	Distribution to individuals, or groups, of educational materials to support clinical care
Provide group education	Courses, workshops, conferences, educational meetings
Provide E-learning	Educational activities that use information and communication technologies
Provide clinical decision support systems	Computerized systems that utilize data analytics within electronic health records to provide point-of-care alerts, prompts and reminders for assisting healthcare providers
Stimulate local consensus processes	Formal or informal local consensus processes, e.g., for agreeing to a clinical protocol to manage a patient group, adapting to a guideline for a local health system or promoting guideline implementation
Use local opinion leaders	The identification and use of identifiable local opinion leaders to promote good clinical practice
Provide individual instruction at the physician’s office (e.g., outreach visits)	Personal visits by a trained person to health workers in their own settings, to provide information, instruction and support, with the aim of changing practice
Provide feedback	Provision of a summary of clinical performance over a specified period of time to individuals, or groups
Provide reminders	Prompts to perform specific actions at the point of care, including computer decision support systems
RESTRICTIVE STRATEGIES TO IMPROVE ANTIMICROBIAL PRESCRIBING	
Formulary restriction	Strictly limiting which drugs are available to prescribers at a given institution
Pre-authorization	Preapproval of drugs obligatory before dispensing
Automatic antibiotic stop order	Stop dates are automatically applied to an antimicrobial order when therapy duration is not specified

A number of these strategies have also been described in IDSA stewardship guidelines[1,2]. **Persuasive (i.e., enabling) strategies** (e.g., post-prescription review and advice, education, feedback, reminders) are distinguished from **restrictive strategies** (e.g., pre-authorization, restricted formulary)[76].

The advantages and disadvantages of **pre-authorization** (a frequently used restrictive strategy) and "**post-prescription review and advice**" (a frequently used persuasive strategy) are shown in **Table 5**.

PRE-AUTHORIZATION

Pre-authorization refers to the practice of requiring **approval before prescribing** certain restrictive use antibiotics. Pre-authorization is performed by AMS team members and requires continuous availability of an expert to give approval. This strategy has been shown to improve antibiotic use, but can lead to delay in treatment, increased administrative burden and potential dissatisfaction of prescribers.

Table 5. Advantages and disadvantages of pre-authorization and post-prescription review and advice

Adapted from Dellit *et al. Clin Infect Dis.* 2007;44(2):159–771; Barlam *et al. Clin Infect Dis.* 2016;62:51-772; Chung *et al. Virulence.* 2013;4(2):151-5777.

PRE-AUTHORIZATION	POST-PRESCRIPTION REVIEW AND ADVICE
Examples of advantages	
Prevents unnecessary/inappropriate initiation of antibiotics	Increases visibility of ASP and helps to form professional relationships
Ensures optimal empirical therapy	Maintains autonomy of prescribers
Prompts review of clinical parameters, patient history and prior cultures before initiating antimicrobial therapy	Provides a higher chance for educational opportunities
	More easily accepted by clinicians as it reflects the daily decision-making process
	Frequency can be tailored based on resources available to the ASP
Examples of disadvantages	
Has little effect on post empirical therapy	Compliance is voluntary
Loss of prescriber autonomy	Labour intensive
May delay initiation of therapy	Success is dependent on how feedback is communicated to prescribers

Some common improvement strategies are described in more detail below.

POST-PRESCRIPTION REVIEW AND ADVICE

Post-prescription review refers to prospective **review of antibiotic therapy** in individual patients by AMS teams at some point after the antibiotic has been prescribed. This ideally involves continuous review of the appropriateness of prescriptions, combined with advice where needed. This type of monitoring is also called "**prospective audit with feedback**"[78].

Conducting post-prescription review and advice is a labour-intensive and time-consuming activity. **Monitoring a selection of "critical" prescriptions** remains the most effective approach, e.g., some critical patient categories, certain restrictive use antimicrobial drugs or (intravenous) treatment duration.

FEEDBACK

Feedback is often preceded by an audit and involves providing healthcare professionals with information about their prescribing practices and outcomes over a specified period of time. This process **fosters awareness and encourages adherence** to guidelines. The effect of feedback is greater when it comes from a trusted source, is easily comprehensible, is provided in both oral and written forms, and when the feedback includes specific goals as well as an action plan[79,80].

EDUCATION AND RAISING AWARENESS

Education is a key component of any ASP. Increasing professionals' knowledge and understanding of how antibiotics should be used to treat common infections, and why inappropriate use may lead to resistance and loss of effective treatments is essential and contributes to appropriate antibiotic use practices.

Education of professionals on appropriate antibiotic use should be part of:

- undergraduate curriculum;
- internships;
- professional training for new staff;
- continuing professional development for all prescribers;
- postgraduate education.

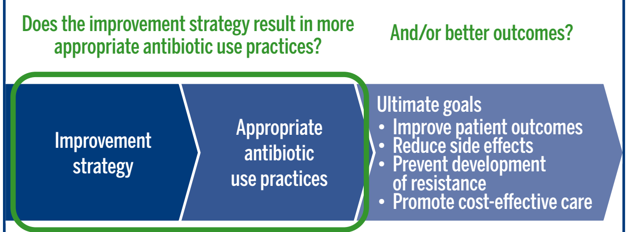
Education should be adapted to each level and aimed at competencies in generic antimicrobial prescribing and stewardship. It should include core concepts in microbiology, pathogenesis and diagnosing infections, antimicrobial prescribing and AMS[81,82].

5.2 Effectiveness of improvement strategies

A key question for AMS teams, of course, is **which improvement strategy works best** to incite professionals to actually use antibiotics appropriately? **(Figure 15)**.

Figure 15. Does stewardship work: the evidence base of the ‘How’ of AMS

Reproduced with permission from Hulscher *et al. Clin Infect Microbiol*. 2017;23:799-805[37]



In a Cochrane systematic review[76], the effectiveness of different interventions to improve antibiotic prescribing practices for hospital inpatients (221 studies, 120 interventions) was reviewed. The effect of **persuasive (enabling) strategies** was assessed separately from restrictive strategies.

It was concluded that:

- Both enablement and restriction can be effective;
- there were high levels of heterogeneity of effect size;
- enablement consistently increased the effect of interventions, including those with a restrictive component;
- feedback further increased intervention effect but was used in only a minority of enabling interventions.

Other systematic reviews also concluded that there is **not one improvement strategy that always works**[37]. This finding is not unique for antibiotic use; reviews in the field of clinical and health services research consistently show this result.

> **There is NO “One size fits all” solution to improve antibiotic use practices**

How then to select from the range of strategies the one that will work best in a specific setting?

> **An inventory of determinants (barriers/facilitators) and behavioral theories should guide the AMS team’s choice of a potential strategy to improve antibiotic use practices**

A more detailed stepwise approach to improvement is described in **Chapter 6**.

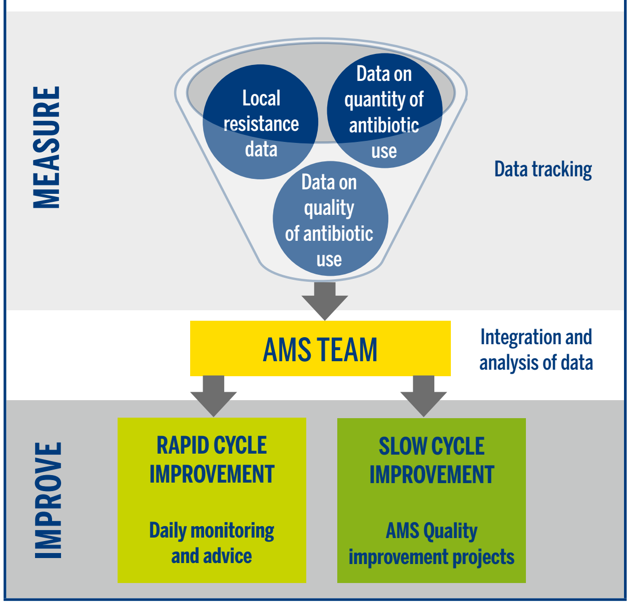
5.3 Improvement strategies in clinical practice

In daily practice, the activities of hospital AMS teams can be broadly divided into two types of improvement strategies **(Figure 16)**.

- **Daily monitoring and advice**, which can be seen as a continuous “**rapid cycle**” improvement (individual level improvement).
- **Quality improvement projects**, which can be seen as “**slow cycle**” improvement (group level improvement).

Figure 16. Schematic representation of hospital AMS team’s activities, differentiating between rapid cycle improvement and slow cycle improvement

Reproduced with permission from the Dutch Masterclass on Antimicrobial Stewardship syllabus



DAILY MONITORING AND ADVICE

Daily improvement activities of AMS teams consist of monitoring and advice for a selection of patients. This can also be referred to as continuous **post-prescription review and advice** (also called "prospective audit with feedback"). Prescriptions to be reviewed should be selected in consensus for:

- **critical diagnosis** (e.g., *S. aureus* bacteremia, candidemia);
- **critical antimicrobial drugs** (e.g., previously defined restricted use antibiotics);
- or **critical antimicrobial treatment objectives** (e.g., IV-oral switch or de-escalation).

Alerts signalling potential inappropriate antibiotic use should be defined, added and escalated to the AMS team by the team members.

Having an electronic patient file that integrates **microbiological, prescribing and clinical data** greatly facilitates stewardship activity by enhancing patient selection and alerts.The alerts are integrated in the AMS team daily activities and meetings. The necessary **actions** are coordinated by the different members of the AMS team **(Figure 17)**.

AMS QUALITY IMPROVEMENT PROJECTS

Effective improvement requires a **systematic approach and good planning**. In the improvement process, the "**Knowledge to Action cycle**"[83] could be used. Antimicrobial stewardship is a continuous cyclic improvement process. A **stepwise approach** is described in **Chapter 6**.

Figure 17. Schematic representation of daily monitoring and advice by AMS teams

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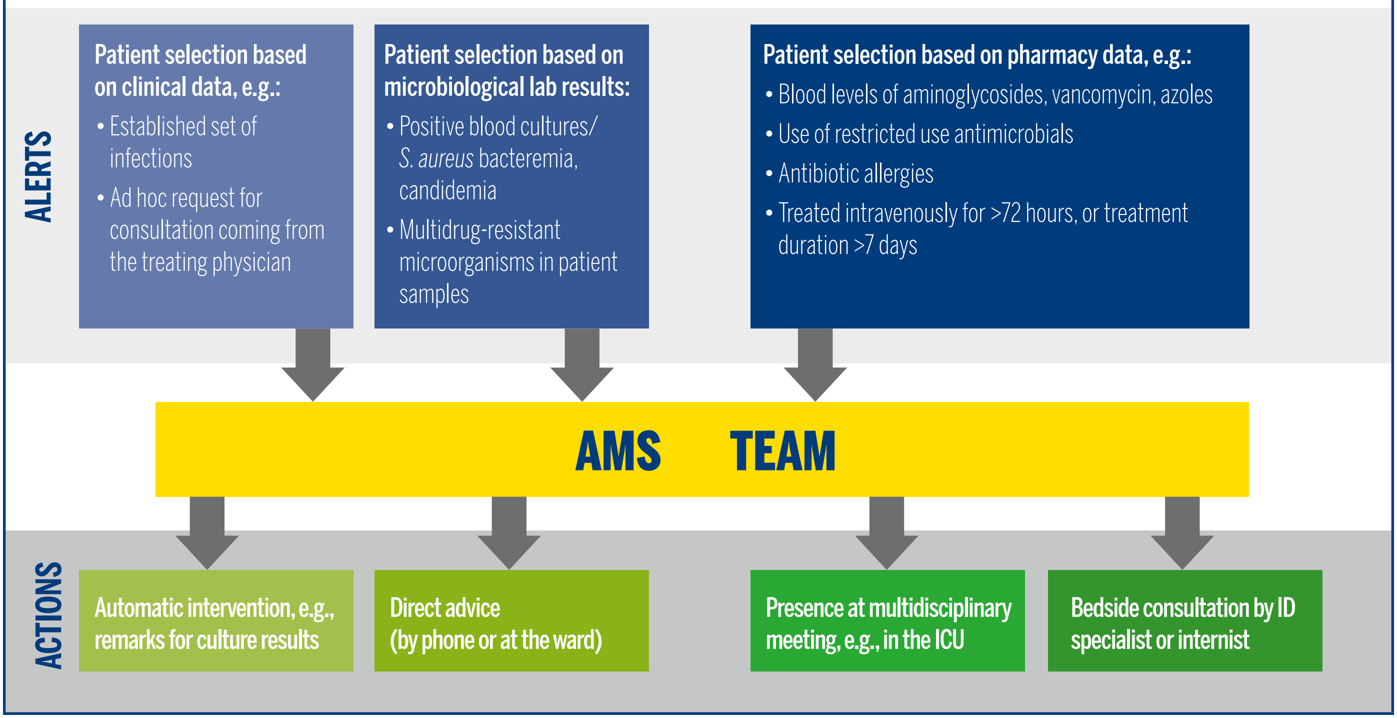


6

IMPROVING ANTIMICROBIAL USE THROUGH BEHAVIOR CHANGE

IMPROVEMENT STRATEGIES of ASPs are reliant on **changes in the behavior of individual prescribers.** In this respect, **behavioral sciences are key** to successful AMS strategies to improve antibiotic use practices **(Figure 18).**

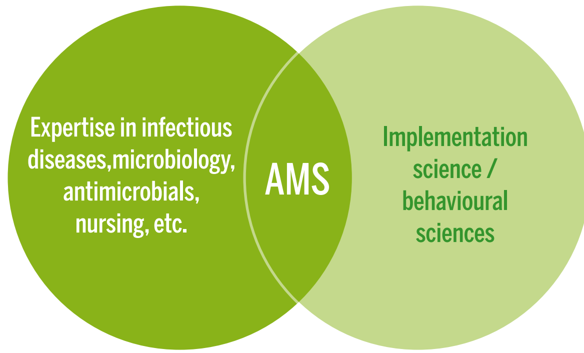
6.1 Behavior change

Behavioral sciences use principles of psychology and sociology, anthropology and economics, to identify and map determinants of behavior to observed practice, and include several models that explain why people behave in certain ways[85,86].

Behavior change theories and models can serve to guide the planning and execution of AMS improvement strategies[87,88].

Figure 18. Areas of expertise required for improvement of antibiotic use practices

Kindly provided by B. Skodvin and I. Smith, adapted from Batalden et al. *J Qual Improv*. 1993;19(10):424-47[84]

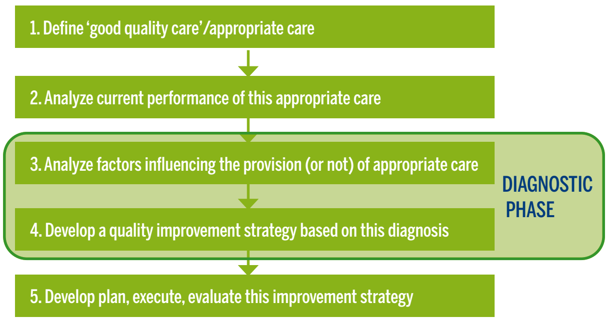


There are many different theories on how to change behavior, but what they have in common is the assumption that a strategy is more likely to be successful in changing behavior if it **addresses the factors/determinants that help or hinder the performance of the recommended behavior**.

What the various theories also have in common is that they suggest a **systematic stepwise approach to change.** A model for planning behavior change, that integrates various theoretical approaches to change, describes **5 crucial steps**[89] as shown in **Figure 19**.

Figure 19. Model for planning change

Reproduced with permission from the Dutch Masterclass on Antimicrobial Stewardship syllabus, adapted from Grol R. *BMJ*. 1997;315:418-421[89]



For AMS, this 5-step model can be used as follows:

1. **Define appropriate antibiotic use practices**, as described in one or more of the ASP objectives (the "What") (Chapter 3).
2. **Measure the appropriateness of one or more current antibiotic use practices** to identify areas most in need of improvement (Chapter 4).
3. **Analyse determinants (barriers/facilitators)** for each of the selected current antibiotic use practices (this Chapter).
4. **Select and build an AMS improvement strategy** to address the determinants that were identified in step 3 (this Chapter).
5. **Execute the improvement strategy and remeasure** (as in step 2) to check whether antibiotic use practices have improved (Chapter 5).

➔ The literature shows that people are inclined to jump from step 2 - when a problem is identified - to step 5, where the problem is fixed. In doing so, they miss out on the **most crucial part of the model**: the "**diagnostic phase**". This phase is described in more detail in the next sections.

An inventory of determinants (barriers/facilitators) and behavioral theories should guide the AMS team's choice of potential strategy to improve antibiotic use practices

6.2 Analyzing determinants of current antibiotic use practices

Step 3 in Figure 19 is about identifying the determinants that help or hinder the improvement of each of the selected antibiotic use practices. These determinants (also referred to as **facilitators and barriers**) of current antibiotic use practices should ideally be explored and addressed systematically. It is important to realize that determinants may be different for different contexts. When exploring determinants, it is crucial to perform a diagnostic analysis for each antibiotic use practice separately as each practice may elicit its own pattern of barriers/facilitators.

Flottorp *et al.* developed a comprehensive, integrated overview of 57 potential determinants (barriers/facilitators) categorized into seven domains **(Table 6)**.

➔ This checklist can be used by AMS teams when exploring determinants.

Table 6. Flottorp checklist of determinants of professional practice

Adapted from Flottorp *et al. Implementation Science.* 2013;8:35[90] CC BY 2.0

DETERMINANTS OF PRACTICE	EXAMPLES
1. Guideline/innovation factors	Source, quality of evidence, feasibility
2. Health professional factors	Knowledge, awareness, skills, intention, motivation, self-efficacy
3. Patient factors	Patient needs, preferences, beliefs, motivation
4. Professional interactions	Communication, team processes, referral
5. Incentives and resources	Materials, financing, information, education
6. Capacity for organisational change	Mandates, authority, leadership, rules, priorities
7. Social, political, legal factors	Healthcare budget, contracts, legislation, influential persons, corruption

* For a more complete overview of determinants, see 'Additional file 4 TICD Checklist – definitions, questions an and examples' accompanying the Flottorp paper

To explore determinants that influence a specific practice in a specific hospital or ward, interviews with individual or groups of professionals, questionnaires and/or observations can be performed. The selection of professionals for interviews or questionnaires depends on the specific practice that is explored. In general, all professionals who are to some degree involved in the practice of interest should be selected.

6.3 Developing a quality improvement strategy

To implement **Step 4 in Figure 19** and improve antibiotic use practices, many **improvement/implementation strategies** can be used[91], often in combination (see Chapter 5).

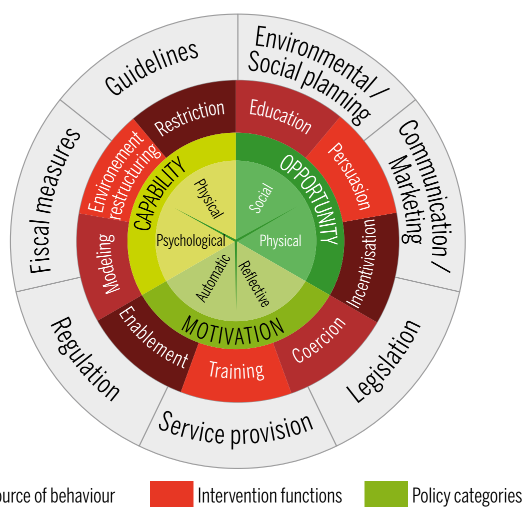
As stated in the previous section, **determinants** should inform the choice of improvement strategies. For example:

- If professionals indicate they have **insufficient knowledge or skills** to perform the recommended antibiotic prescribing practice, **education** should be chosen.
- If professionals indicate that **forgetting** to apply the recommended practice is the problem, then **reminders** should be chosen.
- If **organizational constraints** hinder the performance of the recommended practice, an **organizational process redesign** should be chosen.

To select a strategy that matches the prevailing determinants, several methods and tools can be used, varying from very theoretical approaches, such as intervention mapping, to more pragmatic approaches[90,92-94]. For example, Flottorp *et al.* developed worksheets and a Checklist **(Table 6)** to help guide the choice of the intervention[90]. Another example is the Behavior Change Wheel[93] **(Figure 20)**.

Figure 20. Behavior change wheel

Adapted from Michie *et al. Implementation Science.* 2011;6:42[95]. CC BY 2.0.
More details available from: www.behaviourchangewheel.com



THE KEYS TO SUCCESS

These essential take-home messages offer some keys to the success of a hospital-based Antimicrobial Stewardship Program.

1	Ensure that most **essential prerequisites are met** that make up the base of any good ASP (Chapter 2).
2	Establish a **local antibiotic prescription guideline** that provides treatment advice for common infections which can serve as a normative framework for the AMS team to assess the quality of antibiotic use within the hospital (Chapter 2 and 3).
3	Measure the **quality of antibiotic use** to identify antibiotic use practices in need for improvement and to evaluate the impact of stewardship improvement strategies (Chapter 4).
4	Perform an **inventory of determinants (barriers/ facilitators)** of prescribing behavior and use behavioral theories to guide the AMS team's choice of strategies to improve antibiotic use practice (Chapter 6).
5	Engage the healthcare professionals targeted by the AMS team throughout the process of measuring and improving antibiotic use practices. **Their commitment is crucial** for success.
6	Improving antibiotic use practices requires **persistent effort** in terms of measurement and improvement (Chapter 5).
7	Ensure **early or short term wins** and then consolidate success while progressing with more complex challenges.

CASE STUDY

Reducing empirical ceftriaxone use for community-acquired pneumoniae (CAP) in an internal medicine (IM) department

Based on the project report of Francisco Almeida for the ESCMID* AMS certificate program. Kindly provided by Francisco Almeida MD, Centro Hospitalar de São João, Portugal.

Full report and other examples can be reviewed on the following website: https://www.escmid.org/education/ams-certificate/

This project was motivated by local data from our hospital. A previous study performed in the hospital analyzed **450 consecutive ceftriaxone empiric prescriptions** from January-May 2021 and found that **half were inappropriate** and that most of that inadequate use was for CAP in the IM department[96]. Therefore, we decided to perform an intervention aiming to **reduce empiric ceftriaxone use for CAP by 50% over 6 months** in the IM department.

STEP 1. Define appropriate antibiotic use practices

Both national (2011) and local (2019) guidelines are available for the treatment of CAP. These guidelines recommend the use of ampicillin or amoxicillin, with or without clavulanic acid, either in monotherapy or combined with azithromycin according to the severity of the infection. Ceftriaxone is featured only as an alternative for penicillin-allergic patients.

STEP 2. Measure current performance of antibiotic use practices

To assess current performance, we chose the following **qualitative (1) and quantitative (2) indicators** for patients with CAP admitted to the IM department:

(1) Percentage of CAP patients empirically started on ceftriaxone

(2) Ceftriaxone LOT for CAP /1000 discharged patients

We also collected data for **balanced indicators** to try to assess the safety of our intervention:

(3) Percentage of CAP patients empirically started on broad-spectrum antibiotics

(4) In-hospital all-cause mortality among CAP patients during the study period

(5) Median LOS in days for CAP patients during the study period

* ESCMID: European Society of Clinical Microbiology and Infectious Diseases

A **one-month audit** was performed (February 2023) and found empiric ceftriaxone use in 21% of the 60 patients identified with CAP **(Table 1)**.

Table 1- Baseline audit

INDICATOR	BASELINE (Feb/23, n=61)
Empiric ceftriaxone use for CAP	13/61 (21.3%)
Ceftriaxone LOT /1000 discharged patients	86.1
Empiric broad-spectrum use for CAP	14/61 (23%)
All-cause in-hospital mortality (CAP patients)	18%
Median LOS of CAP patients	7 days

STEP 3. Analyze determinants (barriers and facilitators)

We chose a **focus group approach** to discuss barriers and facilitators with the senior prescribers in each of the 4 IM sectors, and asked them the following two questions:

(1) Which are the main barriers to using protocol first-line antibiotics for CAP over ceftriaxone?

- Most prescriptions are made in the emergency department (ED) and attending teams are reluctant to change them.
- Some practitioners do not trust our protocol's first line choices for CAP.
- Ceftriaxone can be given once per day and there is no need for renal adjustment.
- The protocol is not widely known inside the IM department.
- Some IM practitioners are not aware of the disadvantages of using ceftriaxone over protocol first-line antibiotics.

(2) Which resources can be used to improve the use of protocol first-line antibiotics for CAP over ceftriaxone?

- Most practitioners in the department are motivated to improve their practices regarding antibiotics.
- All four sectors hold weekly reunions where good clinical practices are often discussed.
- All prescriptions on admission to the IM department are reviewed by an IM practitioner (either in the ED by IM practitioners on emergency duty or immediately after admission to the IM by the internal residency team).

Barriers were analyzed using the COM-B model[95]:

- Psychological capability (lack of awareness of protocol or of disadvantage of using ceftriaxone);
- social opportunity (reluctance to change prescription started in ED);
- physical opportunity (access to guidelines);
- automatic motivation (lack of habit prescription started in ED);
- reflective motivation (lack of trust in protocol options, convenient posology).

STEP 4. Develop the improvement strategy

The improvement strategy consisted of:

(1) An **initial presentation** focusing on:

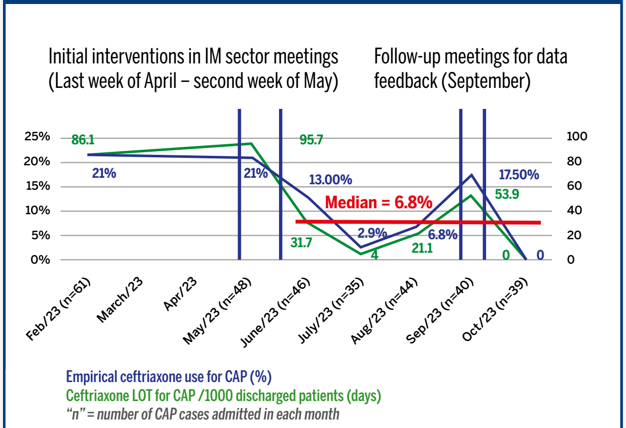
- **Education** (to address reflective motivation, psychological capability): local CAP epidemiology and protocol first-line options were discussed.
- **Persuasion** (to address reflective motivation, automatic motivation): disadvantages of using ceftriaxone over first-line options, local epidemiology showing increasing gram-negative resistance and plans for future audit of ceftriaxone prescriptions with data feedback were discussed. Early switch from protocol first-line options to oral therapy were proposed as an alternative to the posology commodity of ceftriaxone.
- **Modelling** (automatic motivation, social opportunity): prescribers were invited to give their opinion, reinforce protocol-compliant practices and encourage active revision of prescriptions started in the ED.

(2) **Follow-up presentations** in September and November with **data feedback** using the indicators described above.

The improvement strategy also integrated the **facilitators** proposed in the focus group:

- IM sector meetings were used as a platform for the intervention.
- The team's motivation for good practices was used to determine the tone of messages and to ask role models to provide their opinion.
- Since all ED-initiated prescriptions would be reviewed by IM practitioners, it was not necessary to involve the ED teams, enabling resources to be focused solely on intervening in the IM department.

Figure 1. Evolution of result indicators



STEP 5. Execute and evaluate the improvement strategy

The same indicators as described in stage 2 were used for follow-up measurements.

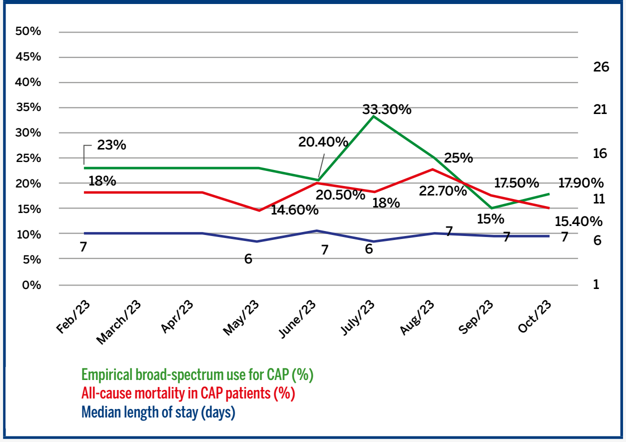
The **intervention and data collection** took place from May-October 2023 (**Figures 1 and 2**).

- In May, the proportion of CAP patients empirically started on ceftriaxone remained at 21%.
- From June to October, a steady decrease towards a median of 6.8% was observed.
- Ceftriaxone LOT for CAP/1000 discharged patients showed a similar trend.
- An initial increase in all-cause mortality and the proportion of CAP patients empirically treated with broad-spectrum antibiotics was observed, however, the median from June-October was 17.5% and 19.6% respectively, similar to the initial audit.

Our intervention **achieved the goal of a 50% decrease of ceftriaxone use for CAP** and did not show signs of increasing adverse outcomes.

This project allowed us to test an **effective and well-received way of designing AMS interventions** driven by data and **focused on behavior changes** and was the pilot for new similar projects already underway.

Figure 2. Evolution of balanced indicators



ADDITIONAL RESOURCES

USEFUL RESOURCES FOR EDUCATION AND TRAINING IN ANTIMICROBIAL STEWARDSHIP (accessed on July 30, 2024)

- **WHO on-line course - Antimicrobial stewardship: a competency-based approach.**
  Access: https://openwho.org/courses/AMR-competency
- **WHO Antimicrobial Stewardship Programs in health facilities in low- and middle-income countries: A WHO practical toolkit**
  Access: https://iris.who.int/bitstream/handle/10665/329404/9789241515481-eng.pdf?sequence=1
- **WHO AWaRe Handbook**
  Access: https://iris.who.int/bitstream/handle/10665/365135/WHO-MHP-HPS-EML-2022.02-eng.pdf?sequence=1
  Access to tool: https://aware.essentialmeds.org/list
- **CDC on-line course: Antibiotic Stewardship**
  Access: https://www.train.org/cdctrain/training_plan/3697
- **Ebook- Antimicrobial Stewardship: From Principles to Practice. British Society for Antimicrobial Chemotherapy [BSAC]**
  Access: https://bsac.org.uk/antimicrobial-stewardship-from-principles-to-practice-e-book/
- **Open Online Course on Antimicrobial Stewardship. BSAC with University of Dundee and FutureLearn**
  Access: https://www.futurelearn.com/search?q=antimicrobial-stewardship
- **Antimicrobial Stewardship (AMS), Volume 2, 1st Edition.**
  Access: https://shop.elsevier.com/books/antimicrobial-stewardship/pulcini/978-0-12-810477-4
- **CIDRAP web-based resource: Antimicrobial stewardship project with emphasis on news, commentary, webinars, podcasts**
  Access: http://www.cidrap.umn.edu/asp
- **The Behaviour Change Wheel: A Guide To Designing Interventions**
  Access: https://www.behaviourchangewheel.com
- **Global Point Prevalence Survey led by the University of Antwerp**
  Access: https://www.global-pps.com
- **The Dutch Antimicrobial Stewardship Masterclass**
  Access: https://www.radboudumc.nl/en/education/courses/dutch-antimicrobial-stewardship

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