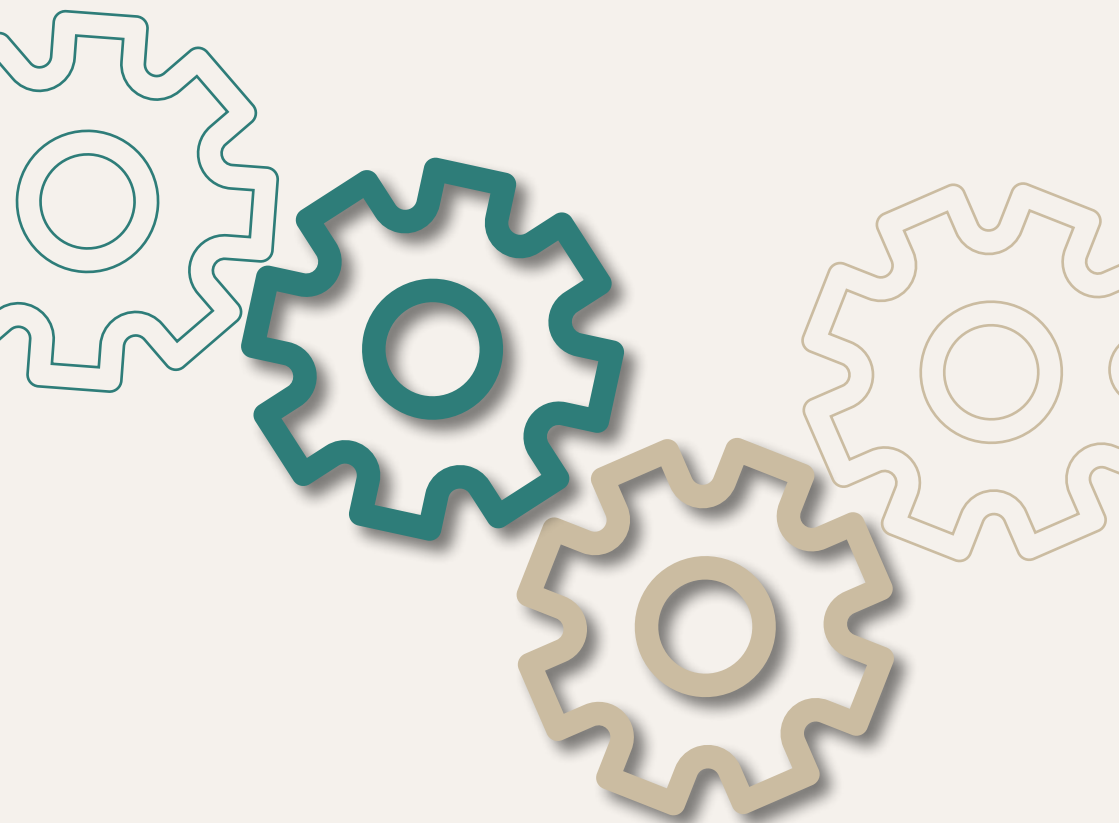


Antimicrobial stewardship interventions: a practical guide



**World Health
Organization**

REGIONAL OFFICE FOR

Europe

Antimicrobial stewardship interventions: a practical guide

Abstract

Antimicrobial resistance (AMR) is a global public health emergency. Antimicrobial stewardship programmes have been identified as one of the core strategies to tackle AMR. How to select the most appropriate interventions for each setting however remains challenging. This practical guide describes 10 commonly used stewardship interventions, which promote the optimal use of antimicrobials at health care facilities. Administrators, health care leaders and front-line clinicians learn about the most common interventions, the evidence behind them, as well as important implementation considerations, particularly for low-resource settings.

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Acronyms

AMR	antimicrobial resistance
AWaRe	Access Watch Reserve [classification system]
CLSI	Clinical and Laboratory Standards Institute
CNS	central nervous system
ICU	intensive care unit
PCN	penicillin
WAAW	World Antimicrobial Awareness Week

Introduction

Introduction: Antimicrobial resistance (AMR) is a global public health emergency. AMR is the ability of a microorganism to survive and resist exposure to antimicrobial drugs, threatening the effectiveness of successful treatment of infection.

There are different types of antimicrobials, which work against different types of microorganisms, e.g. antibacterials or antibiotics against bacteria, antivirals against viruses, antifungals against fungi, etc.

Antimicrobials are life-saving drugs and their discovery is among the most important scientific advances of the 20th century. There is, however, accumulating data demonstrating that antimicrobial misuse is widespread in all health care settings. The misuse of antimicrobials in human health care is one of the key modifiable drivers of the emergence of AMR. *Antimicrobial stewardship* in this practical guide refers to coordinated interventions designed to promote the optimal use of antibiotic agents, including the decision to use them, drug choice, dosing, route, and duration of administration.

Objective: This practical guide describes some commonly used stewardship interventions, which promote the optimal use of antimicrobials at health care facilities. Although evidence to support these interventions is primarily from studies conducted in high-income countries, this guide highlights ways to adapt these interventions to resource-limited settings.

Target audience: The target audience are administrators and health care leaders who are new to antimicrobial stewardship and are planning to implement one or more interventions in their health care setting. Clinicians interested in antimicrobial stewardship may also use this document as a reference.

Scope: There are 10 interventions in this practical guide, six of which occur prior to or at the time of prescription and four of which occur afterwards. They are listed in Table 1 and there is a summary sheet for each intervention. Although this list is not comprehensive, the selected interventions are those that are commonly deployed, and their impact has been assessed in the medical literature.

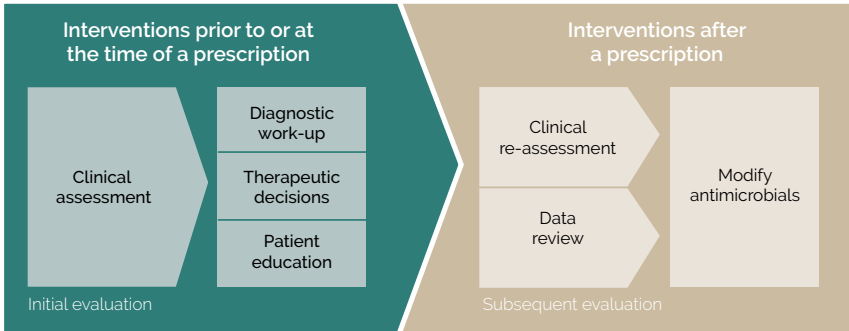
Table 1. List of 10 interventions in this compilation

Interventions prior to or at the time of prescription	Interventions after prescription
1. Clinician education	7. Prospective audit and feedback
2. Patient and public education	8. Self-directed antibiotic reassessments (antibiotics timeouts)
3. Institution-specific guidelines for the management of common infections	9. Dose optimization
4. Cumulative antibiograms	10. Duration optimization
5. Prior authorization of restricted antimicrobials	
6. De-labeling of spurious antibiotic allergies	

Relevance to clinicians: Front-line clinicians play a vital role in protecting the power of antimicrobials. In the OpenWHO online course, "Antimicrobial Stewardship: A competency-based approach"¹, it was illustrated how clinicians can improve their antibiotic prescribing by using *the clinician-patient encounter* as a framework. These steps in clinical decision-making, depicted in Fig. 1, will be familiar to clinicians. Although the timing may differ in the outpatient and inpatient settings, the general flow of decision-making is similar. The interventions reviewed in this practical guide target different stages in the clinician-patient encounter.

1 Read more: Antimicrobial Stewardship: A competency-based approach [website]. In: OpenWHO/courses. Geneva: World Health Organization; 2016–2021 (<https://openwho.org/courses/AMR-competency>, accessed 24 February 2021).

Fig. 1. Steps in clinical decision-making



Examples of how to use the practical guide are:

- as a reference when planning to implement an antimicrobial stewardship intervention; and
- as a tool for educating colleagues and clinicians at your institution about antimicrobial stewardship.

Barriers to antimicrobial stewardship: The barriers to appropriate antimicrobial prescribing are numerous and complicated. However, antimicrobial stewardship interventions can overcome these obstacles and be highly effective. The summary of each intervention calls attention to some of the barriers and how programmes can successfully overcome them. Some commonly cited barriers are:

- clinician knowledge deficits regarding the optimal use of antibiotics;
- opposition from clinicians to antimicrobial stewardship;
- limited access to reliable clinical diagnostic or microbiologic testing;
- limited or unreliable access to quality-assured antimicrobials;
- fear that withholding antimicrobials, and especially antibiotics will lead to poor outcomes;
- limited or lack of communication between health care providers;
- limited infrastructure and/or administrative support for antimicrobial stewardship programmes or interventions;
- limited access to data, including antimicrobial prescribing trends, at a facility, and of data regarding the prevalence of AMR in the community;
- limited public/patient acceptance of antimicrobial stewardship; and
- public access to antimicrobials, such as antibiotics, without prescriptions in the community.

Where to start?

This depends on your institution's resources.

If your facility has limited access to microbiologic data, consider the following interventions:

- clinician education
- patient and public education
- institution-specific guidelines for the management of common infections
- duration optimization.



If your facility has access to timely and accurate microbiology results from a microbiology laboratory, also consider:

- cumulative antibiograms
- self-directed antibiotic reassessments (antibiotic timeouts).



If your facility employs clinical pharmacists, consider:

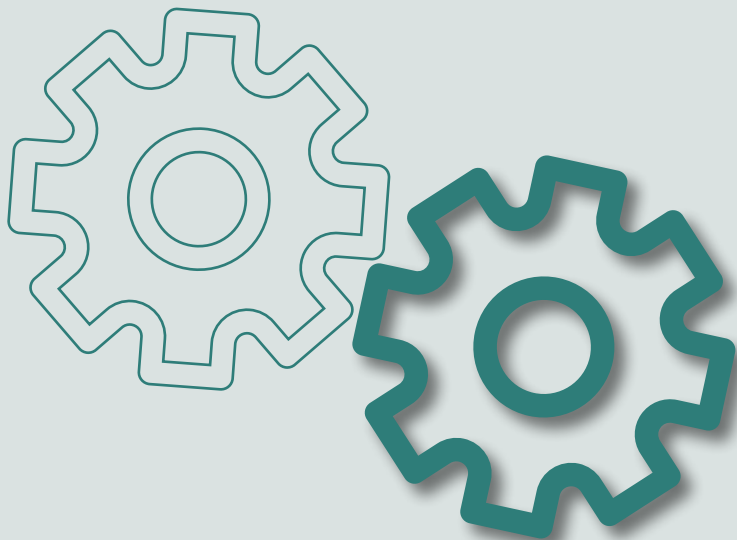
- dose optimization.



If your facility is planning to or has established an antimicrobial stewardship team with dedicated time to review patient cases, consider:

- prior authorization of restricted drugs
- prospective audit and feedback
- de-labeling of antibiotic allergies .

Interventions **prior to** or
at the time of prescription





Clinician education

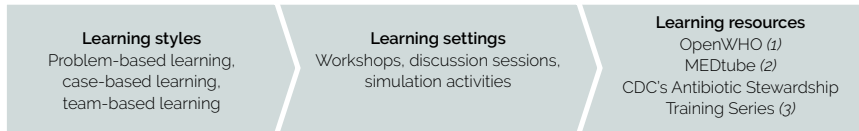
Ongoing clinical education by physicians is essential for the provision of optimal patient care. It is crucial for policy-makers and health care administrators to provide opportunities for physicians to address information gaps through clinical education and continuing professional development. New treatments, optimal diagnostic tools and strategies, and practicing the right prescribing behaviours – all with the focus on patient care and safety – remain the cornerstones of excellence in clinical practice and are essential for successful antimicrobial stewardship. Clinical education can occur in many formats, all of which offer different advantages for stewardship training but incur different costs.

Rationale for implementing the intervention

- The intervention is essential for maintaining knowledge of up-to-date practices and guidelines for the use of antimicrobials.
- Clinician education enhances awareness of local, regional and global threats from AMR.
- Attention to ongoing clinical training is an important aspect of patient safety in health care services delivery.

Diverse educational materials can be used to address different prescriber learning styles. Stewardship education can be accomplished in a variety of settings. New programmes or stewardship initiatives with limited resources should leverage existing open access material to create meaningful clinical education opportunities for prescribers (Fig. 2).

Fig. 2. Diverse educational resources employed in continuing medical education



Prerequisites

Engaged clinicians are needed, who are interested in maintaining up-to-date clinical education, for their own knowledge and to encourage peers.

Strong leadership is needed to support prioritization and to ensure protected time for clinicians to engage in continuing education and professional development. Leadership can also help by incentivizing human resources to maintain up-to-date clinical knowledge.

Supporting evidence

- In a study by Doron & Davidson (4), a significantly greater decrease in annual prescription rates for antibiotics occurred in the educational intervention group vs the control group and the effect was sustained during a subsequent four month follow-up period. The educational interventions included lectures, didactic meetings, email memos and telephone counselling by an expert.
- In a study by Regev-Yochay et al. (5), educational interventions, such as group meetings, workshops, seminars, and practice campaigns, resulted in a decrease in the total antibiotic prescription rates in children treated by physicians who attended those educational interventions, compared to control physicians (observed in the first intervention year).
- In a study by Weiss et al. (6), the distribution and presentation of user-friendly educational materials (guidelines) to physicians and dentists in Quebec significantly reduced antibiotic prescribing compared with the rest of Canada.



- Behavioural interventions were shown to reduce inappropriate prescribing in multiple settings. In primary care, peer comparison and accountable justification reduced inappropriate antibiotic prescriptions for acute respiratory tract infections, most of which are viral (7,8).

When should you choose this intervention and for which settings is it appropriate?

- Clinical education is appropriate to all clinical practice settings and all levels of training.
- Facilities with limited resources can develop clinical educational material on a limited number of institutionally relevant stewardship topics.
- Clinical education is often combined with other stewardship interventions to provide an in-depth rationale for certain approaches (e.g. training in pharmacokinetics/pharmacodynamics) enhances understanding of antimicrobial prophylaxis).

Risks/costs

Risks/costs include:

- a lack of time to pursue continuing professional development;
- a lack of available educational materials for a broad audience;
- concerns about local applicability of mass educational programmes; and
- psychological barriers of individual clinicians towards engaging in some of the educational interventions (e.g. the fear of not knowing enough).

Examples of educational exercises

1. On the occasion of the annual World Antimicrobial Awareness Week (18-24 November), organize an educational event addressing the prudent use of antibiotics targeted at one or more of the following types of audience:

- (I) physicians (junior and/or senior)
- (II) health care professionals in general
- (III) students
- (IV) patients.

You can use this opportunity to conduct a questionnaire among the target groups in order to assess their level of awareness about AMR, hand hygiene and antibiotic stewardship practices. These data could be used in the future for research purposes or to establish an ongoing clinical education agenda.

2. Within your clinical practice, discuss team cases involving antimicrobial treatment that you encountered which posed diagnostic or treatment challenges. In your presentation try to include:

- (I) Signs and symptoms
- (II) Laboratory results
- (III) Imaging performed
- (IV) Treatment (especially current guidelines)
- (V) Outcomes and follow-up
- (VI) Prophylaxis

Encourage the presentation of cases by different team members on a regular basis. Make it a recurring session of meetings and discussions. Consider interdisciplinary case conferences which may include discussion with other departments within your institution (e.g. case conference on joint pulmonary/critical care and infectious diseases).

3. Organize mini-review seminars with your clinical team to discuss recent updates on treatment guidelines for infections related to your department. Encourage all team members (e.g. nurses, physicians, students) to be involved in planning the content and delivering information updates at regular intervals (quarterly/annually).

NOTE: Formal (surveys) and informal (comments from attendees) feedback should be part of the routine evaluation of clinical education exercises to assess the utility of educational offerings for the target audience. Information from these surveys can be reviewed with leadership in order to ensure appropriate resource allocation.



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Patient and public education

Patients and the public should be educated about the proper use, administration, storage and disposal of antimicrobials, such as antibiotics, so they can become allies in the fight against AMR. This education can take two explicit forms: 1) mass education campaigns which inform the public, such as informational messaging about influenza and the fact that antibiotics do not treat viral infections; and 2) direct clinician to patient education targeting a specific medical condition. Both types of education increase overall public awareness of AMR and work to counter the rampant misinformation and misconceptions about antibiotics in the public sphere.

Rationale for implementing the intervention

AMR is a global problem. The solution requires individual, local, national and international solutions. Collective awareness of this problem by patients and the public at large is an important part of stemming the tide of AMR.

Prerequisites

- *Human resources:* Clinical and non-clinical personnel need time to develop and implement a communication strategy at a specific institution. It is helpful if those charged with patient/public education missions can assess what the patients/public already know about AMR and adapt messaging accordingly (e.g. access to community survey data or national antimicrobial utilization trends can enhance targeted messaging to certain populations). Consider integrating messaging about AMR with other local health education campaigns (e.g. importance of vaccines, food safety and hand hygiene).

- *Technical/Implementation resources:* Free material accessible on the Internet may need to be adapted to the local context. For example, teams may need resources to adapt materials for specific patient populations (e.g. pediatric/adolescent patients, parents; patients with different languages). Higher-order technical support to develop visual or multimedia material is an advantage but not a necessity. Web-based content, including the use of social media, may be utilized, including materials developed by WHO, such as those dedicated to World Antimicrobial Awareness Week (WAAW) (see links below).
- *Support of leadership:* Dedicated commitment from the administrative leadership, regarding the importance of AMR messaging to patients and the public, can vastly extend the reach of your message.

Relevant literature

- General information is available on public awareness and responsibility in the judicious use of antibiotics (1).
- The problem that there is limited public knowledge about antibiotics and AMR is global and affects the full spectrum of patients, from pediatric to adult care (2-4).
- Communicating your message about AMR is complex and needs to be done in the context of other important and related health messaging (5).
- Training and involvement can be supported by multiple participants in the health care system (6).
- Online pledges can increase public and health care professional engagement with the problem of AMR (7).



Consider the message you would like to share

Public education on antimicrobial use can take many forms. It is important to provide a consistent, easily understood, evidence-based message about appropriate antimicrobial use that is also supported by all stakeholders involved in your educational campaigns (e.g. local leaders, patient advocates, community members, physicians, nurses). Examples of key concepts on which you may focus your education campaigns, and which have been included in many stewardship initiatives, include:

- How do antibiotics work?
- What types of diseases and conditions can antimicrobials treat?
- How does antibiotic resistance develop?
- When should I take antibiotics?
- Why is it important to follow instructions on the duration and dosage of antibiotic therapy?
- What should I do with leftover antibiotics?
- How are antibiotics used outside of human medicine?
- What else can I do to reduce my risk for diseases that antibiotics cannot reduce? (e.g. importance of vaccines for vaccine-preventable diseases)

Each patient visit is an opportunity to touch on one of these important aspects of AMR education. Encourage patients to ask questions and clarify what they do not understand. Create a safe space for sharing their doubts and worries concerning the use or avoidance of antibiotics.

Examples of WHO campaigns and other useful interactive materials



World Antimicrobial Awareness Week (8)

Hand Hygiene Day, 5 May. An example of WHO campaign "Save lives: Clean Your hands" (9)

World Immunization Week 2019 (10)

Messages for the general public regarding AMR (11)

An interactive website with awareness activities produced for World Antibiotic Awareness Week (12)

Superbugs: the game to play on smartphone or tablet (13)

A comic book in Spanish "Superheroes against Superbugs: Antimicrobial Resistance" (14)

YouTube video: Stop the superbugs (15)

Educating patients about antibiotic use (16)



When should you choose this intervention and for which settings is it appropriate?

- *Hospitals vs ambulatory care:* Patients often stay in the hospital for a long enough time to allow you to have more opportunities to engage in educational interventions and reinforce your message. Patients seen in the ambulatory care setting may be less ill, and more focused on the big picture rather than acute medical conditions, and thus more attuned to accept educational information. Additionally, ambulatory patients may have a better-established relationship with clinicians, making it easier for them to receive AMR information and repeat messaging. Patients are often accompanied by their families in both settings which may help improve retention of the message.
- *Academic setting:* Students can be great educators for patients. They often have more time available to dedicate to one-on-one education. Furthermore, engaging in such educational activities helps to consolidate students' knowledge, develop skills and language necessary for doctor-patient communication as well as build up self-confidence when contributing to crafting pro-health behaviours in the community.
- *Waiting rooms:* These can serve as useful spaces for providing health care information while a patient awaits an appointment and are excellent venues to leverage the use of technology to enhance your message.

Risks/costs

- Patient education is time-consuming and requires repeat messaging.
- Information acquisition may vary across a population based on willingness to accept ideas about AMR and baseline knowledge of basic scientific concepts.
- Certain information about AMR may cause anxiety (e.g. colonization with bacteria producing extended-spectrum beta-lactamases) or fear of stigmatization (among marginalized populations, such as refugees or immigrants).

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Institution-specific guidelines for the management of common infections

Institution-specific guidelines or algorithms can be adapted from national or international evidence-based guidelines to reflect local epidemiology, access to diagnostic testing and drug availability. Attaching programmatic interventions to national guidelines may leverage support at individual institutions, especially when an antimicrobial stewardship programme is new. Common targets for institution-specific guidelines include: respiratory tract infections, skin and soft tissue infections, urinary tract infections, and surgical site infection prophylaxis. Infectious Diseases Society of America guidelines recommend institution-specific guidelines to be coupled with an implementation strategy to encourage awareness and adherence to the guideline (1).

Rationale for implementing the intervention

This intervention:

- allows for standardization and reduced variation of prescribing practices;
- allows for adaptation to local formulary/drug availability and laboratory capabilities;
- provides a benchmark for appropriate antimicrobial use that can be used in audit and feedback;
- allows for targeted educational initiatives; and
- allows for front-line clinicians to be included in developing institution-specific guidelines, thereby increasing the likelihood of its suitability to their circumstances and their adherence to the algorithm when managing patients.

Prerequisites

- *Human resources:* Antimicrobial stewardship teams often coordinate the development of institution-specific guidelines and monitor compliance with guideline recommendations (e.g. prospective audit and feedback).
- *Local expertise:* The utilization of institution-specific guidelines increases when front-line clinicians participate in their development.
- *Support of leadership:* Institutional leadership increases the likelihood that front-line clinicians will participate in the development of and adherence to institution-specific guidelines.
- *Implementation plan:* This may include dissemination of the institution-specific guidelines: in multiple formats (e.g. electronic; hard-copy – including pocket cards); through targeted education initiatives to improve awareness and adherence, or the incorporation of recommendations in the form of order sheets or order sets (electronic or hard-copy). The implementation plan may also include prospective audit and feedback to track adherence to the guidelines.

Supporting evidence

- Institution-specific guidelines (2-9) are associated with:
 - increased appropriate antibiotic utilization (e.g. at diagnosis of an infection);
 - increased use of antibiotics with a narrower spectrum of activity;
 - early switch to oral formulations of antibiotics (from parenteral formulations); and
 - shorter duration of antibiotic therapy.



When should you choose this intervention and for which settings is it appropriate?

- All settings are appropriate, including hospital, long-term care or outpatient settings.
- Both new and experienced antimicrobial stewardship programmes can lead the development of institution-specific guidelines.
- Programmes should start by targeting a common infection that is encountered frequently in their setting and is sub-optimally managed (e.g. inappropriate choice, dose, duration of antimicrobial use, or use of diagnostic testing).
- This intervention is often combined with targeted education and audit and feedback.

Risks/costs

- This includes time associated with developing and updating institution-specific guidelines and monitoring adherence. In many cases, guidelines should be reviewed every 3–5 years and when updated evidence becomes available.



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Cumulative antibiograms

Cumulative antibiograms, or cumulative antimicrobial susceptibility test data, describe the proportion of isolates of a given microorganism that remains sensitive to recommended antibiotic(s) based on *in vitro* susceptibility testing. Local cumulative antibiograms are most useful in guiding empiric antimicrobial choices for common infections at the point of care and can inform the development of local guidelines. In some settings, local front-line prescribers are educated to use cumulative antibiograms to inform empiric antimicrobial decision-making. Over time, cumulative antibiograms can be used to track the emergence of local resistance. However, for this tool to be useful, it must be developed in with established guidelines to ensure its accuracy (1-3). An example is provided in Fig. 3.

Fig. 3. Example of an annual cumulative antibiogram of *E. coli* isolated from urine

No. isolates	Ampicillin	Cefazolin	Ceftriaxone	Cefepime	Ertapenem	Gentamicin	Amikacin	Ciprofloxacin	Nitrofurantoin	Trimethoprim-sulfamethoxazole
4792	56	72	86	90	99	86	92	69	92	70

Percent susceptible to given drug

Source: (4)

Rationale for implementing this intervention

- Antibiotic therapy is often started empirically to provide initial control of a presumed infection of unknown cause. Local cumulative antibiograms can inform which empiric antibiotics are most appropriate for patients with common infections.
- Cumulative antibiograms can inform the empiric antibiotic therapy recommendations included in institution-specific guidelines for the management of common infections.
- Cumulative antibiograms can also provide a broad overview of local antibiotic resistance over time (e.g. the proportion of *Staphylococcus aureus* isolates that are methicillin-resistant).
- Enhanced cumulative antibiograms, as recommended by American guidelines (5), may be more informative than institutional cumulative antibiograms, but can be challenging to produce. *Stratified antibiograms*, including those that are location-specific (e.g. emergency department or intensive care unit) or population-specific (e.g. pediatric or immunocompromised patients), may more accurately describe the risk of infections due to resistant organisms for particular patients (6). *Combination antibiograms* predict the likelihood of resistance to more than one antibiotic and may be more helpful in managing patients at risk of multidrug resistant organisms. For more information, please see the references below.

Prerequisites

- *Human resources*: Developing cumulative antibiograms is time- and labour-intensive, particularly for microbiology laboratory staff. This should be done in concordance with established procedures.
- *Microbiology laboratory*: Cumulative antibiograms aggregate individual culture data. To ensure that these data are not heterogenous, microbiology laboratories must use and demonstrate adherence to standardized protocols with appropriate quality controls for in vitro antibiotic susceptibility testing. In addition, cumulative antibiograms must be developed in a standardized way to ensure validity. For example, Clinical and Laboratory



Standards Institute (CLSI) standards state that antibiograms only include microorganisms for which at least 30 non-replicative isolates were detected. Including organisms with less isolates would generate inaccurate results (7).

- *Free on-demand webinar:* "Preparation, Presentation, and Promotion of Cumulative Antibiograms To Support Antimicrobial Stewardship Programmes" (8,9).
- *Information technology support:* Developing this tool requires database management and support.
- *Implementation plan:* Institutions must be able to produce and promote cumulative antibiograms (e.g. paper or electronic format). Frontline clinicians may require education regarding how best to utilize this tool in their practice.
- *Support of leadership:* The microbiology laboratory will require resources to develop the cumulative antibiogram as described above.

Supporting evidence

- Antibiograms can provide an overview of the emergence of antibiotic resistance in particular settings over time (10,11).
- Combination antibiograms may be particularly useful in managing infections due to multidrug-resistant organisms (12,13).
- Cumulative antibiograms can be an important teaching tool for clinician education (14,15). One group showed that, with specific training, the number of clinicians who reported they used a cumulative antibiogram when determining empiric antibiotics more than doubled.

When should you choose this intervention and for which settings is it appropriate?

- The intervention is appropriate for any hospital with a reliable microbiology laboratory demonstrated by consistent technical performance of *in vitro* susceptibility testing.
- Consider this intervention for hospitals developing local guidelines for the management of common infections to align the antimicrobial formulary and local guidelines with the local susceptibility data.

Risks/costs

- Developing standardized cumulative antibiograms may be time- and resource-intensive.
- Some established guidelines, such as those of CLSI, are available only by purchase (9). However, a free webinar is available (8). Lack of access to established guidelines or protocols to develop cumulative antibiograms will likely yield unreliable and non-comparable results, as has been demonstrated in several studies (16,17).
- Enhanced cumulative antibiograms (e.g. stratified or combination antibiograms) require technical expertise and a sufficient volume of relevant microbiologic data to draw accurate conclusions.

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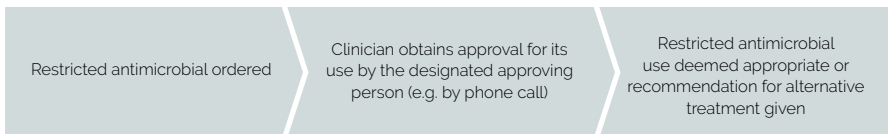




Prior authorization of restricted antimicrobials

Prior authorization of restricted antimicrobials requires that clinicians obtain approval for specific antimicrobials before they are released from the pharmacy for administration to patients. Approval may be granted by antimicrobial stewardship team members, pharmacists, or infectious diseases physicians, including trainees. Preauthorization provides direct control over restricted drugs; however, its disadvantages include impaired prescriber autonomy and potential delays in drug administration. It is one of two core point-of-care interventions recommended by guidelines regarding the implementation of antimicrobial stewardship programmes (1). A schematic of workflow for prior authorization is presented in Fig. 4.

Fig. 4. Schematic of workflow for prior authorization



Rationale for implementing this intervention

- Prior authorization provides direct control over the use of targeted antimicrobials and, among other benefits, provides a mechanism to deal with drug shortages.
- Because approval must be obtained before a drug is released or continued beyond initial dosing, prior authorization allows for the optimization of empiric antimicrobial use.

- Direct communication between front-line prescribing clinicians and those granting approval for the use of antimicrobials allows for personalized education.
- The regular engagement of prescribing clinicians raises the profile of antimicrobial stewardship programmes and builds relationships.

Prerequisites

- *Human resources:* Prior authorization of restricted antimicrobials is commonly performed by the core members of an antimicrobial stewardship team or infectious disease physicians (including those in training). The approval process can be time-intensive and requires real-time access to the person providing approvals in order to avoid delays in antibiotic administration. This may mean allowing for initial dosing to avoid delays in critical cases (e.g. septic shock). Success of this intervention depends on the approver's expertise, motivation and communication skills.
- *Support of leadership:* Institutional leadership support is important when there is disagreement between clinicians and those granting approval for the use of antimicrobials.

Supporting evidence

- Prior authorization of restricted antimicrobials (2-12) has been associated with:
 - decreased targeted antibiotic utilization and cost of targeted drugs;
 - increased appropriate antibiotic utilization;
 - reduced adverse effects associated with antibiotics (5) (e.g. *Clostridium difficile* infections);
 - reduced dosing errors; and
 - improved patient outcomes.



When should you choose this intervention and for which settings is it appropriate?

- Prior authorization is most commonly performed in hospitals and other inpatient settings.
- This intervention should be considered when antimicrobial stewardship teams and/or infectious diseases physicians have sufficient resources to dedicate to this activity, including experienced personnel and dedicated time (1).
- Facilities with limited resources could choose to include only a limited number of targeted antimicrobials or to perform prior authorization only during certain hours of the day (e.g. during regular business hours), allowing for the first dose or first 24 hours of a drug to be administered without approval.
- Prior authorization is often combined with other stewardship interventions, including formulary restrictions and prospective audit and feedback. Programmes may consider using the Access, Watch, Reserve (AWaRe) classification of antibiotics to help determine which drugs to target with restriction or prospective audit and feedback (13).

Risks/costs

Risks/costs are that the intervention:

- is resource- and time-intensive;
- requires clinical expertise and excellent communication skills;
- may lead to an unintended increase in the prescribing of non-restricted antimicrobials; and
- may lead to a loss of prescriber autonomy: If initial dosing is allowed without approval, prescribers may delay prescriptions to "after hours" when approvers are not available to avoid prior authorization.

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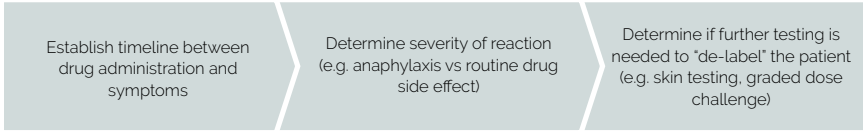
De-labeling of spurious antibiotic allergies

Among the allergies to medications most frequently reported by patients, antibiotics are among those most often implicated. Many of the patients receiving a so-called label of antibiotic allergy, however, do not have clinically significant allergies – or may not have an allergy at all. Labeling a patient with an antibiotic allergy can have a drastic impact on a physician's antibiotic selection for a patient and often leads to overly broad antimicrobial coverage or the use of second-line therapies. In an Australian study, patients labeled with antibiotic allergies were more likely to receive intravenous agents (when there were viable oral options). Allergy-labeled patients were also more likely to get inappropriate therapy or longer duration antibiotic therapy compared to non-allergic patients (1).

This can have significant consequences for patients in terms of outcomes. Efforts to clarify antibiotic allergies through dedicated allergy assessment can separate patients who are unlikely to react to antibiotic challenge compared to those who are at significant risk of an adverse allergic reaction. Skin testing for IgE-mediated allergies is most commonly used to evaluate reported penicillin allergies, although testing for other agents is available in specialized settings.

Performing dedicated antibiotic allergy history-taking, with or without dedicated skin testing to remove false antibiotic allergy reports from patient records, is termed “antibiotic allergy de-labeling” and can be an effective strategy to promote antimicrobial stewardship (see Fig. 5 for schematic of workflow). Patients with a remote history of allergies are the ones most likely to benefit from thorough history-taking and skin testing. This is the result of the fact that many such patients have low-risk allergies (or no true allergy at all) and over 50% may outgrow their allergy after 10 years.

Fig. 5. Schematic of workflow for antibiotic allergy “de-labeling”



Rationale for implementing the intervention

- Improve the ability to use first-line antibiotics, especially related to patients with a reported beta-lactam allergy.
- Reduce antibiotic-associated adverse events ..
- Reduce inpatient length of stay.
- Improve the ability of provider history-taking relevant to antibiotic allergies.
- Save health costs.

Prerequisites

- *Human resources:* Prerequisites include: access to an allergy specialist or to allergy training to initiate the programme, including skin prick and intradermal testing; pharmacy support for the preparation of graded doses and intradermal reagents; and an ability to train other clinicians, including pharmacists, to extend the reach of the programme.
- *Physical resources:* Prerequisites include access to: reagents for skin testing (such as sodium chloride negative control, positive histamine control, and major and minor determinants for penicillin (PCN) prick and intradermal testing); and a support service/environment (including intensive care unit (ICU) level care) to manage critical reactions.
- *Support of leadership:* Prerequisites include: dedicated time to perform testing (in inpatient and outpatient settings); pharmacy and physician/clinician resources to perform skin testing; and support to attend specialized training to learn about skin testing if resources are not available locally.
- *Public acceptance:* Prerequisites include clinician confidence with oral beta-lactam challenge as an accurate assessment of a patient's ability to tolerate other drugs in this class. In addition, patient comfort with a trial of an oral agent after negative skin testing requires a certain basic understanding of



immunology that must be confidently presented by the clinician recommending the oral challenge.

Supporting evidence

- In a review of antibiotic use after the removal of a penicillin allergy label in children with low-risk penicillin allergy symptoms, investigators found a cost savings associated with the use of PCN/derivatives (2).
- Programmes targeting hospitalized patients can successfully reduce inpatient and outpatient use of beta-lactam alternative agents (3).
- Antibiotic allergy de-labeling can improve surgical antimicrobial prophylaxis (4).

When should you choose this intervention and for which settings is it appropriate?

- This intervention is most likely and most readily effectively implemented in moderate- to large-sized hospitals or multispecialty outpatient settings. Examples include: outpatients could be referred for antibiotic allergy testing as part of a pre-operative evaluation for planned surgical procedures; and inpatients could undergo testing as part of discharge planning to ensure appropriate agent selection for any long-term therapy (e.g. treatment of endocarditis or osteomyelitis).
- It is ideal for an academic environment because of the availability of multiple specialty services and access to trainees who may assist with allergy testing and monitoring.
- Locations with access to electronic health records, to review allergy data and target specific patient populations, are also appropriate.

Risks/costs

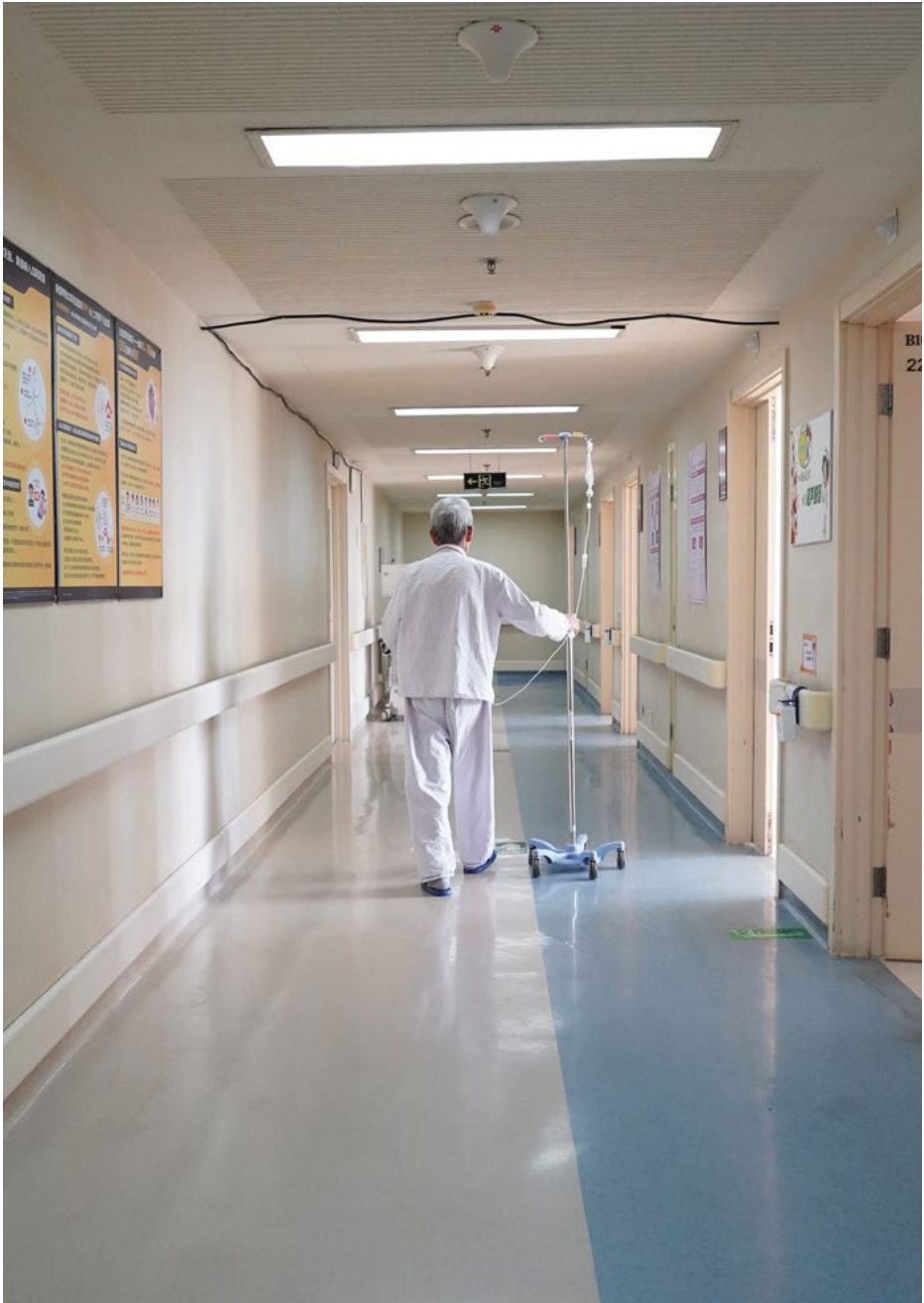
Risks/costs are that the intervention:

- is resource- and time-intensive;
- requires a method for identifying the target patient populations;
- requires clinical expertise such as comfort/familiarity with allergy testing strategies ranging from improved history-taking to intradermal challenge;
- requires significant time for skin prick and intradermal testing, including observation following oral challenge; and
- requires attention/maintenance and education so that allergies are not re-entered into patient records after removal.

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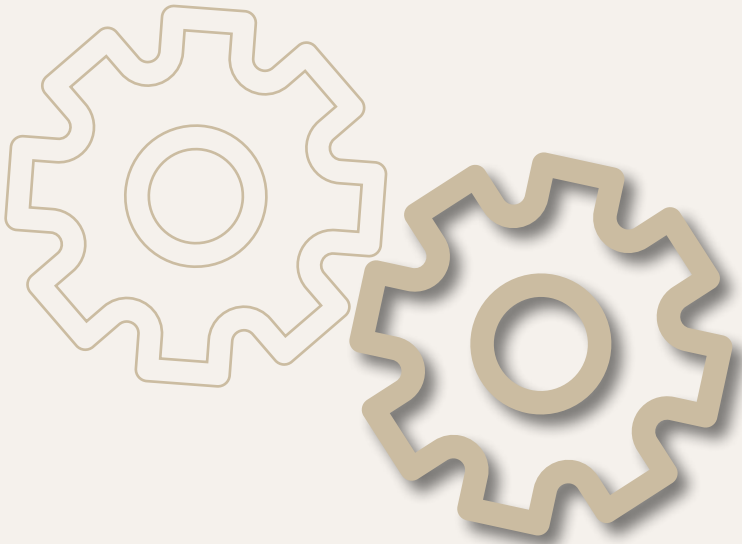
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Interventions
after prescription

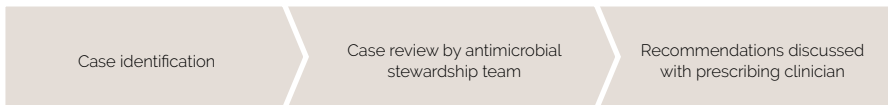




Prospective audit and feedback

Prospective audit and feedback involves the review of active antimicrobial use in individual patients and real-time recommendations to prescribers to optimize therapy. It requires the identification of patients receiving selected antimicrobials, a review of the patient's case by a clinician or pharmacist (typically members of the antimicrobial stewardship programme or team) with expertise in infectious diseases, and engagement with prescribers to antimicrobial recommendations. It is one of two core point-of-care interventions recommended by guidelines regarding the implementation of antimicrobial stewardship programmes (1). A schematic of workflow is presented in Fig. 6.

Fig. 6. Schematic of workflow for prospective audit and feedback



Rationale for implementing this intervention

- Prospective audit and feedback allows for the real-time optimization of antimicrobials for individual patients during their treatment course.
- Communication with the provider caring for a patient allows for personalized education and reinforcement of the principles for prescribing antimicrobials appropriately, which ideally will inform the prescriber's future practice.
- This is most often a persuasive intervention – the antimicrobial stewardship team provides the rationale behind their recommendations in order to convince providers to modify the antimicrobial prescription. This preserves the prescriber's autonomy and allows for collaboration with antimicrobial stewardship programmes.

- Regular engagement of front-line providers raises the profile of antimicrobial stewardship programmes and builds relationships.

Prerequisites

- *Human resources:* Prospective audit and feedback is commonly performed by the core members of an antimicrobial stewardship team. Members of the team differ by clinical settings and medical culture. In the United States of America, national guidelines recommend that core members include an infectious diseases physician and a clinical pharmacist with infectious diseases training. To ensure success, the team conducting prospective audit and feedback must be knowledgeable and have sufficient time to dedicate to this task. A recent assessment among Dutch Antimicrobial Stewardship Teams suggested a methodology to assess the activities and time needed to carry out stewardship activities (2). If clinicians with formal infectious disease training are not available, team members should, as a minimum, have high levels of knowledge in antimicrobial use for infectious diseases. Excellent communication skills are also important when conveying the team's recommendations to front-line providers.
- *Ability to identify appropriate cases:* In settings using an electronic medical record, this is commonly done via computerized surveillance systems or built-in alerts. Other suggestions include using colour-coded stickers on the charts of patients receiving antibiotics as a visual clue to facilitate easy identification, reviewing all patients on specific wards (e.g. intensive care unit) or receiving specific antibiotics (e.g. targeted AWaRe categories.)
- *Support of leadership:* Institutional leadership support increases the likelihood that the antimicrobial stewardship team's recommendations will be accepted by front-line clinicians.
- *Communication with front-line staff:* Engagement with front-line clinicians and nurses before implementing prospective audit and feedback allows for education, garners support, and establishes a workflow to discuss recommendations, such as established meetings or preferred ways of communication.



Supporting evidence

- Prospective audit and feedback is associated with:
 - decreased antibiotic utilization and cost of targeted drugs;
 - increased appropriate antibiotic utilization;
 - reduced adverse effects associated with antibiotics (e.g. *Clostridium difficile* infections);
 - reduced dosing errors; and
 - improved patient outcomes.
- In one cross-over trial, prospective audit and feedback led to larger decreases in antibiotic utilization when compared with a requirement for pre-prescription authorization.
- Prospective audit and feedback has been implemented successfully in a number of settings including large academic hospitals (3), intensive care units (4-6), small community hospitals, children's hospitals (7,8) and skilled nursing facilities (9).



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When should you choose this intervention and for which settings is it appropriate?

- Prospective audit and feedback should be considered when antimicrobial stewardship teams have sufficient resources to dedicate to this activity, including experienced personnel and designated time. Guidelines recommending either prospective audit and feedback or pre-prescription authorization provide the foundation of an antimicrobial stewardship programme.
- This is more commonly done in hospitals or long-term care facilities when antibiotic prescriptions can be readily modified during the course of therapy. This could also be done when microbiologic test results (e.g. urine culture) are available.
- Prospective audit and feedback is often combined with other Antimicrobial stewardship programme interventions, including the development of institution-specific treatment guidelines and formulary restrictions.
- Available resources can dictate the frequency and number of targeted antimicrobials included in prospective audit and feedback. Facilities with limited resources could choose to include only a targeted number of antimicrobials or perform prospective audit and feedback only a few times a week or on targeted units.

Risks/costs

Risks/costs are that this intervention:

- is resource- and time-intensive;
- requires a method for identifying target patient populations (see above);
- requires clinical expertise and excellent communication skills; and
- allows for adherence to recommendations to often remain voluntary.



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Self-directed antibiotic reassessments by prescribing clinicians (antibiotic timeouts)

Self-directed antibiotic reassessments, often referred to as “antibiotic timeouts”, are structured reminders or conversations that prompt clinicians to reassess an antibiotic prescription. Antibiotic therapy is often started empirically to provide initial control of a presumed infection of unknown cause. In practice, however, antibiotics should be periodically reassessed to ensure continued appropriateness. For example, if a specific pathogen is identified as the infecting agent, clinicians can then use this information to adjust the antibiotic prescription to optimally treat the patient (1). However, antibiotics are often not adjusted during a patient’s hospitalization. In one study, including six hospitals in the United States of America, 66% of patients continued to receive the same empiric, broad-spectrum antibiotics on day 5 of their admission (2).

Self-directed antibiotic reassessments, or “antibiotic timeouts”, remind clinicians to reassess antibiotics to ensure continued appropriateness. This intervention can be implemented in a variety of ways (see below).

Rationale for implementing this intervention

- Antibiotics are often not routinely reassessed during a patient’s hospitalization. Self-directed antibiotic timeouts remind busy clinicians to re-evaluate antibiotics, providing an opportunity for antibiotic optimization and improved clinical care.
- Antibiotic timeouts nudge clinicians to adjust antibiotics, without restricting their autonomy.

- Antibiotic timeouts do not necessarily require a formal antimicrobial stewardship team. A formal antibiotic timeout prompts front-line clinicians to re-evaluate an antibiotic prescription themselves. This contrasts with prospective audit and feedback, which is dependent on the antimicrobial stewardship team member to contact the clinician directly and provide antibiotic recommendations, which is labour- and time-intensive. In some situations, other members of the health care team, such as clinical pharmacists or nurses, conduct the antibiotic timeout in conjunction with the clinicians. Ultimately, the decision to alter antimicrobial therapy is made by the prescribing clinician.
- Antibiotic timeouts can also reinforce other principles of optimal antibiotic use, including prompting clinicians to re-evaluate the *dose* and *duration* of antibiotic therapy. *Institutional clinical guidelines* can also be used as a resource for clinicians who are conducting the antibiotic timeout.
- Institutions could prioritize antibiotic timeouts for antibiotics in the AWaRe classification in the "Watch" and "Reserve" categories.



Prerequisites

- *Human resources:* Front-line clinicians should be involved in the development and implementation of antibiotic timeouts to best integrate this intervention into the clinical workflow. Clinicians must also be educated about how to optimally reassess antimicrobials.
- *Access to accurate and timely microbiologic results:* Clinicians use microbiologic data, along with other clinical parameters, to re-evaluate the appropriateness of an antibiotic prescription during an antibiotic timeout. For example, in the management of critically ill patients with sepsis, blood cultures obtained prior to starting empiric broad-spectrum antimicrobials may ultimately identify the causative organism, allowing clinicians to adjust their patient's prescription to a more targeted antimicrobial. Protocols to ensure that appropriate specimens are obtained for microbiologic studies are important to improve the yield and clinical relevance of these tests.
- *Operational support:* There is no one right way to implement this intervention and it can be readily adapted to different settings. Antibiotic timeouts can be implemented in a variety of ways, including through the use of a paper or electronic checklist, prompts after antibiotics have been administered for a certain number of days (e.g. 3 days), prompts within the electronic medical record, or via a structured verbal discussion between the prescribing clinician and another health care provider (e.g. pharmacist). As with all stewardship interventions, it is often helpful to target specific units or wards during the first phase to focus efforts and determine logistics.
- *Documentation:* Decisions made during antibiotic timeouts should be documented to allow for monitoring and evaluation.
- *Support of leadership:* Leadership support is critical to ensuring compliance with this new intervention.

Supporting evidence

- One multicenter quasi-experimental study in the United States found that a single, prescriber-driven antibiotic timeout for patients receiving any antibiotic on days 3–5 of their hospitalization led to a significant but small decrease in inappropriate therapy (45% to 31%), but did not impact overall antibiotic use (3).
- At a Canadian teaching hospital, resident physicians conducted “antimicrobial self-stewardship” audits twice a week on patients receiving one of four targeted antimicrobials, using an online tool. They observed a decrease in the use of these targeted antimicrobials, and this was associated with cost savings, but not overall antibiotic utilization. The online tool also prompted clinicians to reassess dosing and the anticipated duration of therapy (4).
- One United States Veteran’s hospital targeted 2 antibiotics with an antibiotic timeout programme that included an enhanced medical record that facilitated the review of pertinent clinical data, a standardized note to guide clinicians through the timeout, and an educational/marketing campaign. They found that early discontinuation of one of the targeted antibiotics increased after implementation of this intervention (5,6).

When should you choose this intervention and for which settings is it appropriate?

- This intervention is most readily applicable to the inpatient setting.
- Antibiotic timeouts can be self-directed, however, this intervention may be more impactful if paired with other antimicrobial stewardship interventions, such as prospective audit and feedback.



Risks/costs

- This intervention relies on the engagement, compliance and knowledge base of a front-line clinician to perform the antibiotic timeout when prompted and adjust antibiotics appropriately. Some institutions have developed educational material to train clinicians on how to conduct a self-directed timeout.
- There are no data to inform the optimal implementation of an antibiotic timeout, especially in resource-limited settings.
- Antibiotic timeout may be more impactful if combined with other antimicrobial stewardship interventions, such as audit and feedback.

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Antibiotic dose optimization

Antibiotic optimization requires individualized attention to patient characteristics that can influence the appropriate dose, interval and route of administration of an antibiotic used in a given setting. For example, giving too small a dose risks undertreating an infection and engendering resistance, while giving too large a dose can increase the chances for medication side effects. Optimized antibiotic dosing is a stewardship strategy designed to improve outcomes and reduce the negative consequences of antimicrobial use, including patient side effects and minimizing the development of AMR. Individual patient characteristics, such as age, weight, and renal function, are assessed in concert with disease-specific factors, such as location and severity of infection and the targeted pathogen. While this strategy is most often employed at the initial prescription of antibiotics, it can also be used as a strategy for improving antimicrobial use during subsequent patient evaluations. These re-reviews of antimicrobial dosing are particularly important for patients who may have had a significant change from their initial clinical assessment, such as those who are transferred to the ICU or are initiated on hemodialysis/renal replacement therapy.

Rationale for implementing this intervention

- Optimize the use of specific antibiotics.
- Improve overall outcomes for patients.
- Reduce side effects experienced by patients.
- Improve the management of specific conditions (e.g. treatment of meningitis or endocarditis that requires specific dosing).
- Reduce antibiotic utilization and reduce the risk of the emergence of drug-resistant bacteria.

Suggested ways pharmacists and antimicrobial stewardship teams can optimize dosing

Suggested ways include:

- pharmacy protocols (e.g. extended-infusion of beta-lactam antibiotics; aminoglycoside and vancomycin dosing per pharmacy; renal dose adjustments based upon renal function; intravenous to oral conversion on antibiotics when appropriate);
- default dosing for the most commonly used agents;
- guidelines for the management of specific infectious diagnoses;
- using structured order entry with dosing options for intended diagnosis (e.g. doses for meningitis) when antibiotics are initially ordered, either electronically or via paper form; and
- restricted dosing/agents for surgical prophylaxis.

Prerequisites

- *Human resources:* Antimicrobial dose optimization requires access to patient level data by pharmacists who are skilled in integrating clinical, microbiologic and pharmacologic data. This is often a key function of core stewardship team members, such as infectious diseases physicians or clinical pharmacists, with infectious diseases training particularly in pharmacokinetic and pharmacodynamic principles and transition from intravenous to oral agents, and familiarity with antimicrobial susceptibility testing. If an institutional protocol is developed, continued oversight is required to ensure compliance.
- *Support from leadership:* Team members must be provided with dedicated time to perform antimicrobial dosing reviews. Overall support for the stewardship team enhances the likelihood that recommendations will be adopted by other clinicians. For example, leadership support for correct dosing initiatives can increase institutional adoption of these practices.



Supporting evidence

- Patient safety may be improved by the evaluation of pharmacokinetic/ pharmacodynamic parameters for certain drugs and by individualized dose adjustments guided by therapeutic drug monitoring (1-3).
- The dosing needs of specific populations may not be reflected in drug package inserts and could benefit from an individualized approach (4).

When should you choose this intervention and for which settings is it appropriate?

- This intervention is appropriate for all settings. For example, in outpatient settings, dose optimization strategies could focus on a specific population, such as patients with renal impairment. In acute care hospital settings, dose optimization strategies could focus on select patient groups, such as critically ill patients, hemodialysis patients or patients with hepatic failure.
- Locations with access to electronic health records can review dosing data and target specific patient populations or antimicrobials that are frequently mis-dosed (e.g. pediatrics/neonates; obese patients; patients on renal replacement therapy; patients receiving aminoglycosides). Facilities with paper records and manual order entry may be able to review dosing for specific drugs retrospectively and provide physician/ service specific training.

Risks/costs

Risks/costs are that the intervention:

- requires expertise with pharmacokinetics/pharmacodynamics principles;
- requires a consistent method for identifying patient-level data over a treatment course (especially in dynamic situations, such as the dosing of antimicrobials in ICU/critical illness settings); and
- leads to specific dosing recommendations that may not be available for all medications or populations (e.g. hemodialysis patients, hepatic failure patients).

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Antibiotic duration

Selecting the appropriate duration of antimicrobial therapy is of critical importance with regard to the optimal treatment of infections and is a key element in antimicrobial stewardship. Emerging literature favours shorter courses of therapy than have been previously used for several common diagnoses, such as intraabdominal infections and pneumonia, and the duration of therapy is under review for many other clinical syndromes. Several stewardship interventions (addressed elsewhere in this compilation) specifically address the mechanics of optimizing the duration of therapy, such as through the use of guidelines or audit and feedback. Establishing the correct duration of therapy must consider the diagnosis, microbiologic data, the patient's clinical response and the care setting (inpatient vs. outpatient). While an initial estimate of treatment duration should be made on preliminary evaluation, the final duration is more importantly determined at subsequent evaluations when the patient's response to therapy is re-assessed. Giving too short a course of treatment risks undertreating an infection, while giving an unnecessarily prolonged course increases the chances for the selection of resistance and medication side effects. Optimization of antimicrobial treatment duration is a common stewardship strategy and is often considered as part of an overall review of antimicrobial prescriptions based on the principle that appropriate antimicrobial use is achieved through prescribing "the right drug at the right dose and for the right duration". Clinical characteristics, such as patient age, renal function, location and severity of infection, recovered microbe, and mode of drug administration all factor into determining the appropriate treatment duration.

Rationale for implementing this intervention

This intervention:

- decreases antibiotic utilization by eliminating unnecessary days of therapy;
- improves overall outcomes for patients;
- reduces side effects experienced by patients; and

- improves the management of specific conditions (e.g. treatment of CNS infections, endocarditis).

Suggestions for interventions that address appropriate therapeutic duration

Suggestions include:

- incorporating the duration of therapy into clinical guidelines;
- addressing the duration of therapy in audit and feedback interventions;
- embedding a field for the expected duration of therapy in all prescription order forms (this can be adapted to paper or electronic order forms);
- highlighting the duration of therapy as part of clinician education programs (both as a concept and in discussions of treating specific clinical scenarios);
- providing feedback to clinicians who treat common syndromes (e.g. urinary tract infections) for too long, as part of behavioral intervention; and
- using procalcitonin to assist in the decision to discontinue antibacterial therapy when such testing is available.

Prerequisites

- *Human resources:* Stewardship team members require access to patient-level data to establish correct antimicrobial treatment duration estimates. This is often a key function of core stewardship team members, such as infectious diseases physicians or clinical pharmacists with infectious diseases training, and may be codified into institutional guidelines for select diagnoses (e.g. community-acquired pneumonia, urinary tract infections). Team members must also have the ability to communicate with prescribing clinicians at the time of clinical re-evaluation to determine ultimate duration recommendations.



- *Support from leadership:* Team members must be provided with dedicated time to perform antimicrobial duration reviews. Overall support for the stewardship team enhances the likelihood that recommendations will be adopted by other clinicians.

Supporting evidence

- Attention to microbial and other clinical data can shorten the duration of antibiotics, even in critically ill patients, and result in cost-savings (1).
- Shorter duration of therapy may be associated with reduced antimicrobial adverse events and may increase patient compliance (2).
- Attention to appropriate timing and the ultimate duration of antibiotics for surgical prophylaxis can reduce antibiotic consumption without increasing surgical site infections, while reducing superinfections (e.g. CDI) and selection of resistance (3,4).

When should you choose this intervention and for which settings is it appropriate?

- This intervention is appropriate for all settings. For example, in outpatient settings, duration optimization strategies could focus on specific diagnoses, such as community-acquired pneumonia or urinary tract infections. In acute care hospital settings, antimicrobial duration optimization strategies could focus on select patient groups, such as critically ill patients.

Risks/costs

- Data for ideal duration of therapy may not be available for all diagnoses.
- Some duration-truncating approaches rely on clinical improvement and biomarker assessments (e.g. procalcitonin) that may not be available in all clinical settings.
- Patients may not be available for clinical re-evaluation for the consideration of shorter treatment courses (e.g. if discharged from an outpatient setting).

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