



TECHNICAL REPORT

Proposals for EU guidelines on the prudent use of antimicrobials in humans

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Abbreviations

ATC	Anatomical therapeutic chemical
DDD	Defined daily dose
DOT	Day of therapy
EUCAST	European Committee on Antimicrobial Susceptibility Testing
ESAC-Net	European Surveillance of Antimicrobial Consumption Network (ECDC)
FTE	Full-time equivalent
IT	Information technology
SPC	Summary of product characteristics
TATFAR	Transatlantic Taskforce on Antimicrobial Resistance

Introduction

The exposure of microorganisms to antimicrobial agents creates selective pressure that leads to the development of resistance. Inappropriate use of antimicrobial agents accelerates the emergence and dissemination of resistance. Combined with the meagre development of novel antimicrobial agents, the spread of resistance to existing ones is leading to loss of effective options for the treatment and prevention of infections, representing a global health security threat.

Antimicrobials are unique among therapeutic medicines because their use affects not only the person receiving the treatment but also the rest of the population, including other patients, through a complex effect on microbiota in the human host, other animal hosts and the environment. This is one of the main reasons that antimicrobials require a particular focus on targeted measures to promote prudent antimicrobial use at the national and international levels.

In the context of ongoing work against the rising threats from antimicrobial resistance and given the role of antimicrobial misuse and overuse in the emergence and spread of resistance, the European Commission asked ECDC to develop draft EU guidelines on the prudent use of antimicrobials in human medicine, including generic principles of good practice on the appropriate use of antimicrobial agents in human medical practice in the EU.

On 17 June 2016, the Council of the European Union adopted conclusions on the so-called 'One Health' approach to combat antimicrobial resistance, calling on all Member States and the European Commission to develop European Union guidelines on the prudent use of antimicrobials in human medicine to support national guidelines and recommendations.

This technical report is a major ECDC contribution to support the European Commission's goal to finalise EU guidelines on the prudent use of antimicrobials in humans. It draws, among other sources, on Council Recommendation 2002/77/EC of 15 November 2001 on the prudent use of antimicrobial agents in human medicine [1] and on the WHO *Global action plan on antimicrobial resistance* [2].

The goal of controlling antimicrobial resistance can only be achieved by combining strong infection prevention/control and the prudent use of antimicrobials. Infection prevention and control, including vaccination, contributes to a decrease in the number of infections, which leads to lower antimicrobial consumption and fewer opportunities for misuse. The proposals in this document should therefore be seen as complementary to infection prevention and control guidelines.

Definitions

An **antimicrobial** is any substance of natural, semi-synthetic, or synthetic origin that in *in vivo* concentrations kills or inhibits the growth of microorganisms by interacting with a specific target [3]. Antimicrobials with activity against bacteria are called antibacterial agents.

An **antibiotic** is a substance produced by, or derived (chemically produced) from a microorganism that selectively destroys or inhibits the growth of other microorganisms [4]. The term 'antibiotic' is often used to refer to antibacterial agents.

Acquired antimicrobial resistance is the resistance of a microorganism to an antimicrobial agent that was originally effective for treatment of infections caused by this microorganism.

A **multidrug-resistant organism** is a microorganism that is not susceptible to at least one agent in each of three or more antimicrobial categories [5] (NB: two or more antimicrobial categories for *Mycobacterium tuberculosis*).

Antimicrobial therapy can be *empiric*, when based on a reasonable informed clinical judgement regarding the most likely infecting organism or *documented* when the identity and antimicrobial susceptibility of the infecting organism is known as the result of appropriate diagnostic or reference testing.

Antimicrobial prophylaxis is the use of antimicrobials for the prevention of infections.

Prudent antimicrobial use benefits the patient while at the same time minimises the probability of adverse effects (including toxicity and the selection of pathogenic organisms, like *Clostridium difficile*) and the emergence or spread of antimicrobial resistance [6]. Other terms that have been used with the same purpose include judicious, rational, adequate, correct and optimal.

Antimicrobial stewardship embodies an organisational or healthcare system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness [7].

Antimicrobial stewardship programmes refer to coordinated programmes that implement interventions to ensure appropriate antimicrobial prescribing [8].

Prescribers are all healthcare professionals qualified to prescribe antimicrobials. In addition to physicians of all specialties and dental practitioners, the term may refer to prescribing nurses, pharmacists, clinical microbiologists, midwives, and other healthcare professionals, depending on local regulations.

Purpose

The purpose of the proposals presented in this technical report is to provide guidance – based on systematic evidence reviews or expert consensus – on generic elements of good practice on how to prudently and appropriately use antimicrobials in human medical practice. These elements include good clinical practice and the resources, systems and processes that the various authorities and actors should consider when developing and implementing strategies for EU health systems in order to support and promote the prudent use of antimicrobials in human medicine. The target audience comprises all actors who are responsible for, or play a role in, antimicrobial use and whose contribution is necessary to ensure that antimicrobials are used appropriately.

Scope

The proposals in this draft technical report relate to the prudent use of antimicrobials in humans, with a special focus on antibacterial agents. However, all principles mentioned here also apply to other classes of antimicrobials.

The proposals in this draft technical report do not cover specific medical conditions or specific antimicrobials.

Use of the guidelines

These guidelines include measures to be considered by Member States when developing and implementing national strategies to promote the prudent use of antimicrobials and elements of good practice to be followed by healthcare professionals. They also identify activities that may be taken by international organisations and agencies in support of national strategy development and implementation. The wording used in the recommendations (e.g. 'establish', 'ensure', 'consider', 'explore') reflects the strength of the recommendation in relation to the expected benefit, the level of evidence and the applicability in diverse settings. Throughout this document, specific policies, interventions, indicators, medical conditions, and antimicrobials are mentioned as examples to support the design and implementation of the guidelines.

Principles and elements for inclusion in the guidelines

Current evidence and expert opinion support the following elements as effective to support the prudent use of antimicrobials in healthcare:

1. International organisations and agencies

International cross-sectoral, inter-governmental and inter-organisational collaboration and coordination, both within and outside the EU is required to establish standards, systems and procedures necessary to ensure the prudent use of antimicrobials, the sharing of best practices, and the support of capacity development.

International collaboration should contribute to the following goals:

- Facilitating coordination of response to cross-border threats relating to antimicrobial-resistant organisms.
- Designing, implementing and monitoring antimicrobial stewardship interventions and campaigns to support appropriate antimicrobial use and reduce inappropriate antimicrobial use [expert consensus].
Examples: European Antibiotic Awareness Day and World Antibiotic Awareness Week.
- Establish a mechanism for sharing best practice interventions on appropriate antimicrobial use and their impact on relevant qualitative and quantitative outcomes [expert consensus].
- Enabling cooperation on the surveillance of antimicrobial consumption and antimicrobial resistance using a harmonised methodology with the aim of providing timely information regarding cross-border threats from resistant organisms, as well as providing valid and internationally comparable information on resistance and consumption [expert consensus].
- Harmonisation of clinical breakpoints and methods for antimicrobial susceptibility testing [expert consensus].
- The development of good evidence-based clinical practice guidelines that address the most common infections and are adaptable to local resistance patterns and available licensed antibacterials [expert consensus].
- Ensuring access to essential antimicrobials and diagnostic tests by supporting market availability and tackling shortages [expert consensus].
- Encouraging, at the national level, the development of standards and adoption of selective reporting of microbiology results to optimise antimicrobial prescribing [expert consensus].
- Development of evidence-based guidelines on the use of rapid and point-of-care diagnostics [expert consensus].
- Promotion and financial support of research and development of new antimicrobials and new point-of-care tests [expert consensus].
- Ensuring cross-sectoral collaboration in the animal health, food production and healthcare sectors regarding the surveillance of, and policies for, antimicrobial use [expert consensus].

2. National, regional and local governments

National, regional and local governments, have – provided that national competencies have been developed – the ultimate responsibility for developing, implementing, and supporting the policies and infrastructure necessary to ensure the prudent use of antimicrobials. They are also responsible for regulations and auditing the compliance with legal, policy and professional standards. Collaboration with regulators, payers and educators is key to the development and implementation of these policies.

Current evidence and expert opinion support the following as effective elements of national and regional policy, infrastructure and regulatory functions:

Key elements of a national strategy

- Fund, develop and implement a national action plan for appropriate use of antimicrobials in human medicine including multi-faceted interventions adapted to local conditions [9] [expert consensus].
- Introduce antimicrobial stewardship programmes at all levels of care (community, hospital, long-term) [7].
Example: Swedish strategic programme against antibiotic resistance (STRAMA) [10].
- Integrate national antimicrobial stewardship activities with infection prevention/control and vaccination; all activities should be based on the national antimicrobial resistance plans developed in accordance with the cross-sectoral 'One Health' approach [expert consensus].
- Set qualitative and quantitative targets for improvement of antimicrobial prescribing [expert consensus].
Example: antibiotic quality premium (NHS England) [11].
- Ensure timely availability of standardised open data on antimicrobial consumption for benchmarking and on

antimicrobial resistance for informing clinical guidance in the community and hospital sector [expert consensus].

Example: English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) [12].

- Ensure the presence of a mechanism (e.g. a national committee/platform) for the development, implementation and monitoring of clinical guidance for infections; such a mechanism should include diagnostics, treatment/management and infection prevention and control [expert consensus].

Core components and measures for implementation

Clinical guidance

- Ensure availability of national clinical guidance for prophylaxis and management of infections based on national antimicrobial resistance patterns for the community, long-term care facilities, and hospitals [13,14] [expert consensus].
- Develop clinical pathways and provide decision support tools to encourage appropriate testing and management [expert consensus].
- Ensure that national clinical guidance is reviewed and revised when there is a significant change in antimicrobial resistance, or if there is new evidence on the management of infections, or at regular intervals (e.g. every 2 to 3 years); national clinical guidance should take into consideration the last valid summary of product characteristics of a medicinal product (SPCs) [expert consensus].
- Ensure accessibility of the guidelines to all prescribers by providing wide distribution and promotion [expert consensus].
- Ensure availability of guidelines for therapeutic and prophylactic antimicrobial prescribing in dental practice [expert consensus].

Regulation of antimicrobials

- Ensure access to the antimicrobials recommended in clinical guidance, by conducting a review of national market availability, implementing measures to support sustained market availability for both innovative and generic products and tackling shortages. At the same time, limit the use of last-resort antimicrobials to safeguard their effectiveness, by establishing restrictive measures for use [expert consensus].
- Ensure that information on the risks of antimicrobial resistance and inappropriate use of antimicrobials is included in the SPCs and/or in patient information leaflets [expert consensus].
- Review, or establish if not in place, the legal provisions on availability of antimicrobials over the internet [expert consensus].
- Ensure compliance with the regulations with regards to the dispensing of antimicrobials without prescription [expert consensus].
- Explore per unit dispensing of antimicrobials taking into consideration all relevant guidelines and regulations [expert consensus].
- Explore the introduction of special labelling of antimicrobial packages [expert consensus].

Antimicrobial prescribing and stewardship

- Provide guidelines and tools for the implementation of antimicrobial stewardship programmes covering the community, long-term care facilities and hospitals [expert consensus].
Examples: Strategies to enhance the rational use of antibiotics in hospital (Germany), guidelines for antimicrobial stewardship in hospitals (Ireland), practical guide for antimicrobial stewardship (Netherlands), 'Start smart then focus' and TARGET antibiotics toolkit (UK) [13,15].
- Ensure an appropriate number of experts in the field of antimicrobial stewardship through education of a sufficient number of specialists in infectious diseases and clinical microbiology and other professionals [expert consensus].
- Monitor and audit the appropriate use of antimicrobials, including the introduction of relevant quality indicators and systems for monitoring these indicators. Ensure regular feedback of the results to prescribers [expert consensus].
- Ensure the introduction and monitoring of electronic antimicrobial prescribing systems that are preferably able to link clinical indication, microbiological and consumption data [expert consensus].
- Ensure availability of adequate microbiology services and diagnostics, including rapid and point-of-care diagnostic tests [expert consensus].
- Consider and, if appropriate, implement incentive systems for appropriate prescribing [expert consensus] [16].
Examples: Introduction of appropriate prescribing as a certification indicator for healthcare facilities and Pay for Performance (P4P) in primary care (France), antibiotic quality premium (NHS England) [11].
- Fund, design, implement and assess the outcome of national awareness and educational campaigns on antimicrobial use by targeting health professionals and the general public (including children, teenagers, students, the elderly and vulnerable groups) [17].
Example: Eurobarometer surveys.
- Promote behavioural interventions to reduce inappropriate antimicrobial prescribing.
Example: accountable justification and peer comparison [expert consensus] [18].

- Explore motivational and system change approaches to optimise antimicrobial prescribing [expert consensus].
Examples: reimbursement policies to discourage inappropriate prescribing and unnecessary doctor consultations for minor infections [expert consensus] and public commitment (Antibiotic Guardian, UK).
- Identify best practices on antimicrobial promotional activity in collaboration with the pharmaceutical industry, to ensure it aligns with promoting appropriate antimicrobial prescribing [expert consensus].
- Introduce appropriate disposal systems in the community setting, and inform the general public on the correct disposal methods for antimicrobial drugs [expert consensus].

Education

- Make sure that the competency of all healthcare professionals is guaranteed by continuous professional development activities on appropriate antimicrobial use [7,19,20].
Example: require participation in a minimum number of certified educational activities on antimicrobial prescribing and use.
- Ensure that antimicrobial stewardship is included in all specialty training curricula for clinical specialties [expert consensus].
- Include training on prudent antimicrobial use in medical, nursing, pharmacy, dentistry and midwifery schools [expert consensus] [7,21]. This training should include a strong practical component as part of an inter-professional approach.
- Introduce education on prudent antimicrobial use, antimicrobial resistance, vaccination and hygiene in primary and secondary education [expert consensus].
Example: implementation of the e-Bug platform [22].

3. Healthcare facilities (resources, systems and processes)

Healthcare facilities are on the frontline for the implementation of policies and procedures, and for the provision of surveillance and monitoring data, which are necessary to ensure prudent antimicrobial use. They are also a focal point for audits during which a facility is examined for compliance with policy and professional standards.

Healthcare facilities should focus on the following proposals:

- Establish and provide the necessary funding and resources for antimicrobial stewardship programmes in each healthcare facility, linked with the infection prevention and control programme and /or the patient safety programme [23-25].
- Ensure timely access to clinical microbiology laboratory services [expert consensus].
- Utilise validated rapid and/or point-of-care diagnostics for defined patient groups to complement clinical assessment and optimise antimicrobial treatment [21,26-31].
- Ensure information technology support for antimicrobial stewardship activities, including electronic prescription and introduce electronic decision support systems [20,32] as tools to improve antimicrobial prescribing [33].
- Contribute to facility-wide, national and regional surveillance studies and prevalence surveys of antimicrobial resistance and antimicrobial consumption, including molecular epidemiological investigations [expert consensus].
- In community/ primary care:
 - Ensure that antimicrobial stewardship activities are in place, under the coordination and with active involvement of the healthcare professionals in these settings, as dictated by the level of care, identified areas of antimicrobial overuse and misuse, and by national and local provisions [expert consensus].
Example area of antimicrobial overuse and misuse in primary care: respiratory tract infections.
 - Establish a multi-faceted approach including elements such as clinic-based education, patient information leaflets [34] and posters, pharmacist counselling of patients on antimicrobial treatment, prescriber feedback and clinician training [32] in communication skills.
 - Ensure sufficient time for consultation to allow for proper assessment and counselling of patients [expert consensus].
- In hospitals, the elements of antimicrobial stewardship programmes should include:
 - An antimicrobial committee or similar formal organisational structure with senior management support [expert consensus].
 - An antimicrobial stewardship team including ideally a clinician with training, expertise and professional involvement in the diagnosis, prevention and treatment of infections (if possible an infectious disease specialist), a hospital pharmacist and a microbiologist (if possible a clinical microbiologist). The composition of the team is dictated by the hospital size and level of care and by national and local provisions [7,20].
 - Salary support and dedicated time for antimicrobial stewardship activities [expert consensus].
Example: 0.5–1.5 full-time equivalents (FTEs) per 250 acute care beds [35,36].
Example of indicator: number of FTEs for antimicrobial stewardship activities.

- Guidelines for the diagnosis and management of infections and for perioperative antimicrobial prophylaxis [expert consensus] [20].
Example of indicator: proportion of prescriptions for selected diagnoses compliant with guidelines.
- Documentation in the patient records of indication, drug choice, dose, route and duration of treatment [7].
Example of indicator: proportion of antimicrobial treatment courses with documentation of indication in the notes, among all antimicrobial treatment courses.
- A policy for preauthorisation and/or post-prescription review [7,21,37].
- Microbiology laboratory services for acute care hospitals should be provided on a 24/7 basis for critical specimens [expert consensus].
- The availability of facility-specific cumulative susceptibility reports for common bacterial pathogens against antibiotics that are recommended in the relevant treatment guidelines [expert consensus] [20].
- An audit of perioperative antimicrobial prophylaxis indication, choice, timing and duration [expert consensus].
- An annual report on antimicrobial stewardship activities which includes an evaluation of effectiveness, reported to the management [expert consensus].
- Monitoring of quality indicators and quantity metrics of antimicrobial use with feedback to prescribers and prescriber actions agreed [7,20].
Example of indicators: defined daily doses (DDDs) or days of therapy (DOTs) per 100 patient-days.
- In long-term care:
 - Ensure that antimicrobial stewardship activities are in place and are given dedicated time and management support, under the coordination and with active involvement of the healthcare professionals in these settings, as dictated by national and local provisions [38].
 - Establish a multi-faceted approach which includes elements such as education of nursing and medical staff, audits of antimicrobial use, feedback to the prescribers, and targeting identified areas of antimicrobial overuse and misuse [39].
Example area for antimicrobial overuse and misuse in long-term care: asymptomatic bacteriuria.

4. Clinical microbiologists

Clinical microbiologists play a key role in providing diagnostic information. At the same time, they have the expertise required to exercise effective infection control, take steps to prevent antimicrobial resistance and adequately treat infections. Furthermore, they provide advice and guidelines on optimal diagnostic strategies for infections. Clinical roles depend on the setting, clinical training and national provisions. The roles outlined in this section may overlap with those outlined below for infectious disease specialists.

Clinical microbiologists should contribute as follows:

- Ensure that susceptibility testing and reporting are in accordance with treatment guidelines (selective reporting) and European (i.e. EUCAST) and national standards [expert consensus].
Example: Selective reporting for urinary tract infections [40].
- Ensure timely diagnosis and communication of critical results (e.g. blood cultures) [41].
- Provide facility-specific cumulative susceptibility reports for common bacterial pathogens against antibiotics that are recommended in the guidelines [expert consensus].
- Be available to clinicians for counselling on diagnostics of infectious diseases, including correct sampling and interpretation of test results, difficult-to-treat pathogens and complicated infections [expert consensus].
- Clinical microbiologists, as full members of the antimicrobial stewardship team, take on responsibilities that include coordination, planning, post-prescription review and feedback [expert consensus].

5. Infectious disease specialists

Infectious disease specialists are involved in the clinical assessment, investigation, diagnosis and treatment of patients with infections, which also includes the optimal use of antimicrobials. They also provide consultation on the prevention and treatment of healthcare-associated infections, e.g. infections in intensive care units and surgical site infections and therefore play a central role in the prudent use of antimicrobials in the hospital.

Depending on setting, training and national provisions, there may be some overlap in the roles outlined in this section with those outlined above for clinical microbiologists.

Infectious disease specialists should contribute as follows:

- Be available for consultation on diagnostic evaluation and treatment of infectious diseases including difficult-to-treat pathogens and complicated infections, as well as appropriate antimicrobial use [42].
- Infectious disease specialists, as full members of the antimicrobial stewardship team, take on responsibilities that include coordination, planning, post-prescription review and feedback [expert consensus].

6. Prescribers

Prescribers are ultimately responsible for the decision to use antimicrobials in patient care. They also choose the type of antimicrobials used in patient care. Prescribers should therefore be provided with training, guidelines and information in order to be able to exercise prudence in the prescribing of antimicrobials. Information should also be given how prescribers can assess and manage patient expectations.

Prescribers should do the following:

- Ensure that they are familiar with the relevant guidelines and prescribing advice before prescribing an antimicrobial [expert consensus].
- Keep themselves up to date regarding antimicrobial prescribing; this can be achieved by attending training courses, being aware of guidelines, and following guidelines [expert consensus].
- Seek and take advice from specialists regarding antimicrobial prescribing [expert consensus].

When making the decision to prescribe an antimicrobial, prescribers should do the following:

- Make a diagnosis during an in-person patient consultation before prescribing antibiotics, except in exceptional circumstances [expert consensus].
- Ensure that appropriate microbiological samples are taken before starting antimicrobial treatment [7].
- Avoid antibacterial treatment when there is only evidence of viral infection or of a self-limiting bacterial infection [expert consensus].
- Avoid treatment for colonisation without evidence of infection after relevant clinical examination and diagnostic testing [43], unless there is a clear indication in the guidelines [expert consensus].
- Use antimicrobial prophylaxis only when indicated in relevant guidelines [expert consensus].
- Avoid antimicrobial combinations unless there is a clear indication outlined in the guidelines [expert consensus].
Example of indicator: proportion of combination treatments among total number of antimicrobial treatments.

When prescribing an antimicrobial, prescribers should do the following:

- Select an antimicrobial in accordance with relevant guidelines, at an appropriate dose, for the shortest effective duration and with appropriate route of administration (preferably oral if possible) [expert consensus] [7].
- Consider relevant host factors: age, comorbidities (e.g. immunodeficiency), renal and hepatic function, pregnancy, breastfeeding, allergies, presence of prosthetic material, potential drug interactions, body mass index and risk factors for antimicrobial resistance (e.g. history of recent antimicrobial use, history of recent travel) [expert consensus].
- Promote allergy testing for patients with a history of allergic reaction to beta-lactams, as a measure to promote use of first-line antimicrobials in non-allergic patients [21].
- Select an antimicrobial with a spectrum of activity as narrow as possible.
Example of indicator: consumption of beta-lactamase-sensitive penicillins (ATC code: J01CE) expressed as a percentage of the total consumption of antibacterials for systemic use (ATC code: J01) [expert consensus] [44].
- Ensure timely administration of antimicrobial treatment for patients with severe infections.
Examples: sepsis, severe community-acquired pneumonia [45].
- If possible, inform the patient and/or responsible caregiver about the reason for antimicrobial treatment and potential side effects and ensure that the patient understands the dosage and duration of treatment; this improves adherence and increases treatment success [expert consensus].
- If antimicrobial treatment is not considered necessary, give the patient advice about the expected natural history of the illness, the limited or absent benefit of antimicrobial treatment, and the potential unwanted side effects of antimicrobials such as diarrhoea and rash, recommendations for symptom management, as well as advice about actions in case of worsening clinical condition (safety netting) [46].
- Address the patient's expectations, questions and preferences as an essential component of patient-centred care and an effective intervention to promote the prudent use of antimicrobials [47].
- Reassess antimicrobial treatment and consider modification (e.g. de-escalation, discontinuation or switch to oral treatment) after 48–72 hours in hospitals and, in specific circumstances, in other settings in accordance with guidelines [7,20].
Example: Day 3 bundle including antibiotic plan, review of diagnosis, adaptation to microbiology and intravenous-to-oral switch [48-50].
Example of indicator: proportion of documented antimicrobial courses with reassessment after 48–72 hours.

In the community, prescribers should do the following:

- Do not prescribe antibacterials for viral or self-limiting bacterial infections [51].
Example of indicator: seasonal variation of the total antibiotic consumption (ATC code: J01) (in the community) [44,52].

- Consider delayed antimicrobial prescribing with appropriate safety netting for adults or children in specific circumstances and in accordance with guidelines [46,53,54].
Example: delayed antimicrobial prescribing for acute otitis media or acute rhinosinusitis.
- Evaluate symptoms and use scoring systems or symptom checking lists to guide the need for diagnostic testing, antimicrobial treatment and urgent referral [46].
Example: use of Centor score or feverPAIN score and rapid streptococcal antigen testing for sore throat.
- Dentists should prescribe antimicrobials in accordance with guidelines. Antimicrobials should not be used by dentists or other healthcare professionals as a substitute for dental operative intervention [46,53-57].

In hospitals, prescribers should do the following:

- Document in the patient chart: indication, drug choice, dose, route and duration of treatment [expert consensus] [7].
Example of indicator: proportion of antimicrobial treatment courses with documentation of indication in the notes, among all antimicrobial treatment courses.
- Follow guidance for perioperative antimicrobial prophylaxis [expert consensus] [58].
Examples of indicators: rate of compliance with administration of perioperative antimicrobial prophylaxis within 60 minutes before incision, rate of compliance with discontinuation of perioperative antimicrobial prophylaxis within 24 hours after initiation of surgery.
- Enhance timely and adequate source control for surgical infections and discourage using only antimicrobials instead of surgical treatment when there is a clear indication for surgical treatment [expert consensus].
- Evaluate the need for parenteral antimicrobials and switch to oral antimicrobials when possible, all in accordance with available clinical criteria [7,21,50,59].
- Therapeutic drug monitoring is recommended for adjustment of the dosing regimen in accordance with guidelines and in specific circumstances [20].
Example: therapeutic drug monitoring for aminoglycosides, vancomycin and voriconazole [21].

7. Pharmacists

Pharmacists in community and hospital settings have expertise in medicines and are the gatekeepers to the use of antimicrobials. As such, pharmacists can act as an important source of advice and information for patients and prescribers on the safe, rational and effective use of antimicrobials (including on side effects, adherence, adverse drug reactions, cautions & contra-indications, interactions, storage & disposal and rationale for treatment). To this end, they need to be provided with appropriate training, guidelines and information in order to be able to exercise prudence in the prescribing of antimicrobials and manage patient expectations.

Pharmacists should do the following:

- Only dispense antimicrobials with prescription, unless specific provisions allow for regulated dispensation in specific circumstances [expert consensus].
- Ensure that the patient and/or the carer understands the dosage and duration of treatment as this can improve adherence and increase treatment success [expert consensus].
- Promote appropriate disposal of leftover antimicrobials [expert consensus].
- Notify adverse-events related to antimicrobials in accordance with regulations [expert consensus].
- In the hospital setting, the pharmacist is a member of the antimicrobial stewardship team and actively involved in antimicrobial management in the multidisciplinary care team. The role of the pharmacist includes assessing the prescription in accordance with local policies for antimicrobial use; reviewing the antimicrobial duration; counselling on the use of restricted antimicrobials; giving advice on dosage, preparation and administration (especially for special patient cohorts such as children); and advising patients on the proper use of antimicrobials. Pharmacists should also be involved in monitoring antimicrobial use [expert consensus].
- Participate in local, regional or national public health campaigns promoting the prudent use of antimicrobials [expert consensus].
- Provide advice to patients and health professionals with regard to contraindications, drug interactions and food–drug interactions [expert consensus].

8. Nurses

The role of nurses within the clinical team is critical because of their regular contacts with patients and their role in administering medicines. Nurses make sure that antimicrobials are taken according to the prescription; they also monitor the response to antimicrobials (including potential adverse effects). In general, nurses are responsible for the administration of antimicrobials and for monitoring the patient and patient safety.

The role of nurse prescribers is also critical (see preceding section).

Nurses should do the following:

- Be actively involved in antimicrobial management as part of the multidisciplinary care team [expert consensus].
- Ensure timely administration of antimicrobials according to prescription [expert consensus].
- Provide advice and educate the patient on the proper use of antimicrobials [expert consensus].
- Utilise protocols and tools that enable you to independently detect patients with severe infections and then trigger diagnostic and treatment algorithms [expert consensus].
- Remind the clinician to reassess the antimicrobial treatment after 48 to 72 hours [expert consensus].

9. Infection control practitioners

Infection control practitioners play an essential role in the prevention and control of infections, many of which are associated with inappropriate antimicrobial use. Infection control practitioners can therefore support the prudent use of antimicrobials through the provision of advice and peer review.

Infection control practitioners should:

- Ensure coordination and collaboration between antimicrobial stewardship programmes and infection prevention and control programmes by highlighting the essential aspects of appropriate antimicrobial use in the prevention and control of healthcare-associated infections [expert consensus].

10. Public/patients

The knowledge, attitudes and behaviour of the public and patients can be of profound importance in establishing and ensuring the prudent use of antimicrobials, both in terms of expectations and normative pressures that these can exert on healthcare professionals and peers, and their adherence to medication schedules.

With respect to the public and patients, both current evidence and expert opinion support the following measures as effective guidance on the prudent use of antimicrobials:

- Patients and the general public should inform themselves and, where needed, seek information from healthcare providers about appropriate antimicrobial use, antimicrobial resistance and adverse reactions to antimicrobials [expert consensus].
- Use antimicrobials only when prescribed [expert consensus].
- Refrain from using antimicrobials which have not been prescribed such as leftover antimicrobials, antimicrobials prescribed for another person, or antimicrobials obtained without a prescription [expert consensus].
- Return leftover antimicrobials to pharmacies and local collection, in accordance with local disposal regulations [expert consensus].

11. Professional associations and scientific societies

Professional associations and scientific societies represent the healthcare professionals and promote the professional and scientific development of their members, thus influencing clinical and laboratory practice.

Professional associations and scientific societies should:

- Cooperate closely with the regulatory authorities in all relevant domains to ensure that the proposed measures to promote the prudent use of antimicrobials are evidence-based and feasible [expert consensus].
- Promote prudent use of antimicrobials among their members through activities that include guideline development and training [expert consensus].
- Avoid conflicts of interest and commercial considerations [expert consensus].
- Promote and conduct relevant research [expert consensus].

12. Research funders

Research is essential to combat the current levels of, and rising trends in, antimicrobial resistance. In particular, translational research is needed to identify options for improving the ways in which we use existing antimicrobials. Research is also needed to explore how the risk of developing antimicrobial resistance can be mitigated.

Research funders and those responsible for research policy should:

- Promote research that assesses and compares behavioural change interventions for antimicrobial prescribing, taking into account cultural differences, in order to improve our understanding how rational antimicrobial prescribing practices can be achieved [60].
- Promote research on interventional studies for antimicrobial prescribing [expert consensus].

- Research the potential of specific antimicrobials and antimicrobial classes to create a selective pressure toward antimicrobial resistance in microbiota [expert consensus].
- Promote clinical research studies on existing antimicrobials, including pharmacokinetic/pharmacodynamics studies, ensuring that studies sufficiently consider sex/gender and age factors across the lifespan [expert consensus].
- Promote research on diagnostic tools, including rapid and point-of-care diagnostics to support evidence-based guidelines for the role of diagnostics in appropriate antimicrobial prescribing [expert consensus].
- Promote research studies in antimicrobial therapeutic drug monitoring in special populations (e.g. critically ill patients, burned patients, paediatric patients, patients receiving continuous renal replacement therapy) [expert consensus].
- Promote research on educational and awareness interventions which target the public and patients [expert consensus].
- Ensure that available research is properly amalgamated and synthesised through systematic reviews and meta-analyses, to inform clinical guideline development and decision-making [expert consensus].
- Ensure that results from research on antimicrobials and antimicrobial prescribing are translated into practice [expert consensus].

13. Pharmaceutical industry

The pharmaceutical industry is a key partner in the overall effort to ensure the prudent use of antimicrobials. Current evidence and expert opinion support the following as effective elements of guidelines in respect of the role of the pharmaceutical industry in promoting the prudent use of antimicrobials.

Specifically, the pharmaceutical industry should do the following:

- Ensure that marketing and promotional activities are in accordance with the summaries of product characteristics (SPCs) and that SPCs mention the risks of antimicrobial resistance and inappropriate use [expert consensus].
- Ensure that financial incentives within companies are aligned with the stewardship principles laid out above.
- Ensure the monitoring of resistance and off-label use after launching new compounds [expert consensus].
- Engage with national and international policymakers and regulators to support the development of policies that promote appropriate antimicrobial prescribing, including the design of novel reimbursement systems, adaptation of pack size and other processes that contribute to the goals of access and conservation [expert consensus].

14. Diagnostics industry

Diagnostic testing, including testing in microbiology laboratories but also point-of-care and novel diagnostics, provides essential information to avoid unnecessary antimicrobial use and optimise antimicrobial selection.

The diagnostics industry should:

- Collaborate with scientific societies and public health in the development of evidence-based guidelines on the use of tests for the diagnosis of infection, including novel diagnostics and point-of-care tests [expert consensus].
- Support studies on the effect of novel diagnostics on the prudent use of antimicrobials [expert consensus].

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Appendix 1. Methodology

In order to provide comprehensive guidelines we aimed to address all aspects of prudent antimicrobial use that are relevant to human medicine. This covers the following domains: 1) international – organisations, agencies, 2) national, regional and local governments, 3) healthcare facilities, 4) clinical microbiologists, 5) infectious disease specialists, 6) prescribers, 7) pharmacists, 8) nurses, 9) infection control practitioners, 10) public and patients, 11) professional associations and scientific societies, 12) research funders, 13) the pharmaceutical industry, and 14) the diagnostics industry.

ECDC initially conducted a systematic review of published guidelines and systematic reviews on interventions, policies, practices, systems and processes that are effective in promoting the prudent use of antimicrobials in human medicine. Published guidelines and systematic reviews were identified through searches in PubMed, EMBASE, the Cochrane database of systematic reviews (CDSR) and a search of national guidelines at Member State ministries of health, public health agencies and websites of professional associations.

The search strategy in PubMed was: ('anti-bacterial agents'[Pharmacological Action] OR 'anti-bacterial agents'[MeSH Terms] OR ('anti-bacterial'[All Fields] AND 'agents'[All Fields]) OR 'anti-bacterial agents'[All Fields] OR 'antibiotic'[All Fields]) AND ('prescribing'[All Fields] OR 'stewardship'[All Fields] OR ('policy'[MeSH Terms] OR 'policy'[All Fields])) AND ('Guideline'[ptyp] OR 'systematic'[sb]) and yielded 554 items.

The search strategy in EMBASE was: antibiotic OR antimicrobial AND prescr* AND ([cochrane review]/lim OR [systematic review]/lim OR [meta-analysis]/lim) AND ([article]/lim OR [review]/lim) AND [humans]/lim and identified 458 articles. The search strategy in CDSR was: (antibiotic OR antimicrobial) AND (prescribing OR stewardship OR policy) and identified 381 items. The results were reviewed independently by two reviewers.

The AGREE guideline appraisal instrument was used for assessment of the quality of the guidelines, while PRISMA was used as a guide for the assessment of the systematic reviews [61,62]. In total, 43 publications (evidence-based guidelines and systematic reviews) were included in the synthesis of evidence. The reference lists of all selected studies were reviewed to identify additional relevant publications.

In addition to the evidence-based guidelines, expert consensus was used to support recommendations for systems, processes and policies to promote and facilitate prudent use of antimicrobials by all relevant actors, including quality assurance measures. To this end, guidelines and other available relevant documents (e.g. action plans) were consulted for system-level recommendations and relevant ones were proposed for discussion by the expert group [7,13,14,63,64]. Available guidelines were assessed to determine the level of evidence of each included relevant recommendation. Elements of national guidelines that were specific for the setting in a particular country were considered to determine whether they would support a widely applicable recommendation. An initial list of recommendations based on the systematic review of existing guidelines and systematic reviews was drafted to be used as a basis for discussion.

Examples of good practice were provided where possible. Example indicators or metrics that can be used for monitoring appropriate use of antimicrobials and comparisons or benchmarking were proposed based on relevant indicator lists, e.g. the DRIVE-AB project [52], the TATFAR structure and process indicators for antimicrobial stewardship programmes [8], and the ESAC-Net indicators on consumption of antibacterials [44]. A list of the proposed indicators or metrics is provided in Appendix 2.

An initial meeting was organised by the European Commission on 25 May 2016 in Luxembourg with the purpose of informing European stakeholders and Member State representatives and receiving their initial input and comments.

ECDC held an expert meeting on 9–10 June 2016 to solicit input and feedback from a panel of Member State experts who were selected on the basis of experience and research in the field of antimicrobial use in hospitals and the community. An initial list of recommendations was proposed and revised during the expert meeting. The revised recommendations were rated by the experts on a 1–9 Likert scale of appropriateness for inclusion in the EU guidelines. The median rating of all recommendations was ≥ 7 , and disagreement – as measured by interquartile range 25–75 – was low (≤ 3). The recommendations were also rated for the level of supporting evidence. A first draft of the guidelines was open for public consultation until 5 September 2016.

A second meeting with European stakeholders, including professional associations and scientific societies, took place on 16 September 2016 in Stockholm.

Appendix 2. Proposed examples of quantitative indicators

The following table provides examples of quantitative indicators/metrics that may be used to monitor appropriate antimicrobial use.

This is not an exhaustive list. For comprehensive lists of indicators the user is referred to the DRIVE-AB project [52], the TATFAR structure and process indicators for antimicrobial stewardship programmes [8] and the ESAC-Net indicators on consumption of antibacterials [44].

Proposed examples of indicators/metrics	Responsibility level
Consumption of beta-lactamase-sensitive penicillins (ATC code: J01CE) expressed as a percentage of the total consumption of antibacterials for systemic use (ATC code: J01)	National/community care
Proportion of combination treatments among total number of antimicrobial treatments	National/community care
Seasonal variation of the total antibiotic consumption (ATC code: J01) (in the community)	National/community care
Number of FTEs for antimicrobial stewardship activities	Healthcare facility
Proportion of prescriptions compliant with guidelines	Healthcare facility
Proportion of antimicrobial treatment courses with documentation of indication in the notes among all antimicrobial treatment courses	Healthcare facility
Antimicrobial consumption measured in DDDs or DOTs per 100 patient-days (in healthcare facilities)	Healthcare facility
Proportion of documented antimicrobial courses with reassessment after 48–72 hours	Hospital
Rate of compliance with administration of perioperative antimicrobial prophylaxis within 60 minutes before incision	Hospital
Rate of compliance with discontinuation of perioperative antimicrobial prophylaxis within 24 hours after initiation of surgery	Hospital

FTE, full-time equivalent; DDD, defined daily dose; DOT, day of therapy.

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