ECDC DRAFT TECHNICAL REPORT

Proposals for draft EU guidelines on the prudent use of antimicrobials in human medicine

This report of the European Centre for Disease Prevention and Control (ECDC) was coordinated by Diamantis Plachouras.

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Acknowledgements

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THIS DRAFT TECHNICAL REPORT IS SUBJECT TO A PUBLIC CONSULTATION PROCESS. THE RESULT OF THAT PROCESS MAY LEAD TO CHANGES IN THE FINAL REPORT

Stockholm, July 2016

Contents

Abbreviations

DDD	Defined daily dose
DOT	Days of therapy
FTE	Full-time equivalent

Introduction

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

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. These draft guidelines will be a key contribution to support the European Commission in its aim to produce a finalised EU guidelines document.

Definitions

An **antimicrobial** is an agent with activity against microorganisms (viruses, bacteria, fungi or parasites). Antimicrobials with activity against bacteria are called antibacterials. The term 'antibiotic' is often used to refer to antibacterials.

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

Antimicrobial therapy can be *empiric*, when based on a reasonable informed clinical judgement regarding the most likely infecting organism or *definitive* 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 or **appropriate antimicrobial use** aims to benefit the patient while at the same time minimises the probability of adverse effects and promotion of the emergence or spread of antimicrobial resistance.

Antimicrobial stewardship programmes refer to coordinated programmes that implement interventions to ensure appropriate antimicrobial prescribing and effective antimicrobial treatment, in order to limit antimicrobial resistance and to prevent *Clostridium difficile* infections.

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

Purpose

The purpose of this draft technical report is to provide guidance on generic elements of good practice on the prudent and appropriate use of antimicrobials in human medical practice. This includes good clinical practice and the resources, systems and processes that the various authorities and actors should consider in the development and implementation of strategies for EU health systems to support and promote the prudent use of antimicrobials.

Scope

The present report relates to the prudent use of antimicrobials in human medicine, with special focus on antibacterials. However, the principles also apply to other classes of antimicrobials.

The report will not cover specific medical conditions or specific antimicrobials.

Principles and elements for inclusion in guidelines

1. International – organisations, agencies

International cross-sectoral and inter-organisational collaboration and coordination is required to establish standards, systems and procedures necessary to control and prevent the cross-border spread of antimicrobial resistance and to ensure the sharing of best practice and support capacity development. Current evidence and expert opinion support the following as effective elements of international collaboration and cooperation:

a. International collaboration in designing, implementing and monitoring antimicrobial stewardship interventions and campaigns to support appropriate antimicrobial use [expert consensus].
b. Establish a new European platform for sharing best practice interventions on appropriate antimicrobial use and their impact on relevant qualitative and quantitative outcomes [expert consensus].
c. International collaboration on surveillance of antimicrobial consumption and antimicrobial resistance [expert consensus].
d. Scientific societies should support the development of good clinical practice guidelines that are adaptable to local resistance patterns and address the most common infections [expert consensus].
e. Ensure access to essential antimicrobials by supporting market availability [expert consensus].
f. Encourage the development of European and national standards for selective reporting of microbiology results to optimise antimicrobial prescribing [expert consensus].
g. Develop European evidence-based guidelines on the use of rapid and point-of-care diagnostics [expert consensus].

2. National and regional – governments, administrators, public health agencies, professional associations and scientific societies

National and regional bodies play a key role in developing, implementing, and supporting the policies and infrastructure necessary to control and prevent antimicrobial resistance and in the regulation and audit of compliance with legal, policy and professional standards. Current evidence and expert opinion support the following as effective elements of national and regional policy, infrastructure and regulatory functions:

a. Fund, develop and implement a national action plan for appropriate use of antimicrobials in human medicine including multi-faceted interventions adapted to local conditions [1] [expert consensus].
b. Integrate national antimicrobial stewardship activities into the national antimicrobial resistance plans that include infection prevention and control and vaccination, in a 'One Health' approach [expert consensus].
c. Set qualitative and quantitative targets for improvement of prescribing [expert consensus]. Example: antibiotic quality premium (NHS England) [2].
d. Ensure availability of standardised local and national open data for benchmarking [expert consensus].
e. Establish a national committee/platform for the development, implementation and monitoring of clinical guidance for infections [expert consensus].
f. Ensure availability of national clinical guidance based on antimicrobial resistance patterns for the community, long-term care facilities and hospitals [3,4] [expert consensus].
g. Ensure national clinical guidance is reviewed and revised when there is a significant change in antimicrobial resistance, new evidence on management of infections or at regular intervals (e.g. 2–3 years) [expert consensus].
h. Provide guidelines and tools for the implementation of antimicrobial stewardship programmes covering the community, long-term care facilities and hospitals. Example: 'Start smart then focus' and TARGET antibiotics toolkit (UK) [3,5].
i. Ensure availability of guidelines for therapeutic and prophylactic antimicrobial prescribing in dental practice [expert consensus].
j. Establish a list of antimicrobials with restrictive measures for use [expert consensus] [4,6,7].
k. Fund, design, implement and assess national campaigns on antimicrobial use targeting the public and health professionals [8].
l. Explore incentive systems for appropriate prescribing [expert consensus] [9]. 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) [2].
m. Review, or establish if not available, the legal provisions on availability of antimicrobials over the internet [expert consensus].

n. Ensure compliance with the regulations with regards to the dispensing of antimicrobials without prescription and over the internet [expert consensus].
o. Monitor and audit the appropriate use of antimicrobials introducing relevant quality indicators and set up systems for monitoring these indicators. Ensure regular feedback of the results to prescribers [expert consensus].
p. Promote the introduction of electronic antimicrobial prescribing systems able to link clinical indication, microbiological and consumption data [expert consensus].
q. Promote common antimicrobial stewardship programmes covering hospitals, primary care and long-term care facilities at national and regional level [expert consensus].
r. Consider behavioural interventions to reduce inappropriate antimicrobial prescribing. Such interventions include, for example, accountable justification and peer comparison [expert consensus] [10].
s. Explore motivational and system change approaches to optimise antimicrobial prescribing. Example: reimbursement policies to discourage inappropriate prescribing and unnecessary doctor consultations for minor infections and public commitment [expert consensus].
t. Explore per unit dispensing of antimicrobials to match pack size with planned course duration according to national guidelines [expert consensus].
u. Supervise and regulate promotional activity by the pharmaceutical industry, so it contributes to appropriate antimicrobial prescribing [expert consensus].

3. Healthcare facilities (resources, systems and processes for healthcare facilities)

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 control and prevent antimicrobial resistance. They are also a key point in the system for the audit of compliance with policy and professional standards. Current evidence and expert opinion support the following as effective elements of guidelines to be applied at the level of a healthcare facility:

a. Establish and provide the necessary funding for antimicrobial stewardship programmes in all healthcare facilities [11-14].
b. For hospitals, the elements of such programmes should include:
    i. An antimicrobial committee or similar formal organisational structure.
    ii. An antimicrobial stewardship team including at least a clinician (iii) and a pharmacist (iv).
    iii. A clinician with expertise in the management of infections to be responsible for the antimicrobial stewardship team.
    iv. A pharmacist responsible for antimicrobial use.
    v. Salary support and dedicated time for antimicrobial stewardship activities. Example: 0.5–1.5 full-time equivalents (FTEs) per 250 acute care beds [15,16]. Example of indicator: number of FTEs for antimicrobial stewardship activities.
    vi. IT support for antimicrobial stewardship activities.
    vii. Guidelines for the diagnosis and management of infections. Example of indicator: proportion of prescriptions compliant with guidelines.
    viii. Documentation in the patient chart of indication, drug choice, dose, route and duration of treatment [expert consensus]. Example of indicator: proportion of antimicrobial treatment courses with documentation of indication in the notes, among all antimicrobial treatment courses.
    ix. A policy for preauthorisation and/or post-prescription review.
    x. The availability of facility-specific cumulative susceptibility reports for common bacterial pathogens against antibiotics that are recommended in the guidelines.
    xi. An audit of perioperative antimicrobial prophylaxis choice, timing and duration.
    xii. An annual report on antimicrobial stewardship activities.
    xiii. Monitoring of quality indicators and quantity metrics of antimicrobial use with feedback to prescribers and prescriber actions agreed. Example of indicators: defined daily doses (DDDs) or days of therapy (DOTs) per 100 patient-days; proportion of cases of *Staphylococcus aureus* bacteraemia where infectious disease consultation was provided.
c. Promote rapid and/or point-of-care diagnostics for defined patient groups to complement clinical assessment and optimise antimicrobial treatment [17-23].
d. Introduce electronic decision support systems [21] as tools to improve antimicrobial prescribing [24].
e. Ensure timely access to clinical microbiology laboratory services. For acute care hospitals, these services should be provided on a 24/7 basis for critical specimens [expert consensus].
f. Establish a multi-faceted approach that may include elements such as clinic-based education, patient information leaflets [25] and public patient education campaigns combined with clinician training [21] in communication skills.

4. Laboratories

Laboratories play a key role in providing diagnostic information and the expertise required to inform effective control and prevention of antimicrobial resistance. Current evidence and expert opinion support the following as effective elements of guidelines to be applied at the laboratory level:

a. Ensure that susceptibility testing and reporting are in accordance with treatment guidelines (selective reporting), and European and national standards [expert consensus]. Example: Selective reporting for urinary tract infections [26].
b. Ensure timely diagnosis and communication of critical results (e.g. blood cultures) [27].
c. Provide facility-specific cumulative susceptibility reports for common bacterial pathogens against antibiotics that are recommended in the guidelines [expert consensus].

5. Prescribers

Prescribers are ultimately responsible for the decision to use, and the choice of, antimicrobials in patient care, and as such 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. Current evidence and expert opinion support the following as effective elements of guidelines to support and enable prescribers in the control and prevention of antimicrobial resistance:

a. When deciding on the use of antimicrobials, the prescriber should:
    i. for a patient with sepsis, start antimicrobial treatment via the intravenous route within 1 hour of recognition of sepsis [28]
    ii. avoid antimicrobial treatment when there is evidence of viral infection or of a self-limiting bacterial infection [expert consensus]
    iii. avoid treatment for colonisation without evidence of infection [29] [expert consensus]
    iv. use antimicrobial prophylaxis only when indicated according to guidelines [expert consensus]
    v. avoid therapy with combinations of antimicrobials unless there is a clear indication according to guidelines [expert consensus]. Example of indicator: proportion of combination treatments among total number of antimicrobial treatments
    vi. select an antimicrobial in accordance with available guidelines, at an appropriate dose and for the shortest effective duration [expert consensus]
    vii. consider relevant host factors: age, immune status, renal function, allergies, foreign bodies and risk factors for antimicrobial resistance (e.g. history of recent antimicrobial use, history of recent travel) [expert consensus]
    viii. consider 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 [20]
    ix. select an antimicrobial with a spectrum of activity as narrow as possible. Example of indicator: [expert consensus] 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) [30]
    x. 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 according to guidelines. Example: Day 3 bundle including antibiotic plan, review of diagnosis, adaptation to microbiology and intravenous-to-oral switch [7,31,32]. Example of indicator: proportion of documented antimicrobial courses with reassessment after 48–72 hours.
    xi. inform the patient about their antimicrobial treatment
    xii. if antimicrobial treatment is not considered necessary, give patients 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, as well as advice about actions in case of worsening clinical condition (safety netting)
    xiii. 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 [33]
b. In the community:
    i. do not prescribe antibacterials for viral or self-limiting bacterial infections [34]. Example of indicator: Seasonal variation of the total antibiotic consumption (ATC code: J01) (in the community) [30,35]
    ii. consider delayed antimicrobial prescribing with appropriate safety netting for adults or children in specific circumstances and according to guidelines [36-38]. Example: delayed antimicrobial prescribing for upper respiratory tract infections

iii. the use of antimicrobials in patients with self-limiting respiratory infection to prevent suppurative bacterial complications should be discouraged, after accounting for patient-specific factors (e.g. immunosuppression, infants). [39]
iv. evaluate symptoms and use scoring systems or symptom checking lists to guide the need for diagnostic testing, antimicrobial treatment and urgent referral. Example: use of Centor score or feverPAIN score and rapid streptococcal antigen testing for sore throat
v. dentists should prescribe antimicrobials according to guidelines. Antimicrobials should not be used as a substitute to dental operative intervention [40-42].

c. In hospitals:
i. take appropriate microbiological samples before initiation of antimicrobial treatment [expert consensus]
ii. follow guidance for perioperative antimicrobial prophylaxis [43] and, in particular, administer intravenous perioperative antimicrobial prophylaxis within 60 minutes before incision (except when administering vancomycin and fluoroquinolones), prefer single dose of perioperative antimicrobial prophylaxis, and avoid prolonging antimicrobial prophylaxis after the end of surgery [expert consensus]. 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
iii. evaluate the need for parenteral antimicrobials and switch to oral antimicrobials when possible, according to available clinical criteria [7,14,20,44]
iv. in high-risk patients, avoid the use of antimicrobials that are associated with increased risk for *Clostridium difficile* infection if there are alternatives [14,20,45]. Example of indicator: incidence of *Clostridium difficile* infections
v. therapeutic drug monitoring is recommended for adjustment of the dosing regimen according to guidelines and in specific circumstances. Example: therapeutic drug monitoring for aminoglycosides and vancomycin [20].

6. Pharmacists

Pharmacists are the gatekeepers to the use of antimicrobials and can act as an important source of advice and information for patients, and as such 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. Current evidence and expert opinion support the following as effective elements of guidelines to support and enable pharmacists in the control and prevention of antimicrobial resistance:

a. Do not dispense antimicrobials without prescription, unless specific provisions allow for regulated dispensation in specific circumstances [expert consensus]
b. Ensure that the patient understands the dosage and duration of treatment and promote returning leftover antimicrobials to the pharmacy [expert consensus].

7. Nurses

The role of nurses within the clinical team, and in particular their regular contact with patients and their role in administering medicines, can be critical to ensuring that antimicrobials are taken according to the prescription and for monitoring the response to antimicrobials (including potential adverse effects). The role of nurse prescribers is also critical and is covered in the preceding section). Current evidence and expert opinion support the following as an effective element of guidelines to support and enable nurses in the control and prevention of antimicrobial resistance:

a. Be actively involved in antimicrobial management as part of the clinical team by acting as the link with the pharmacy, being responsible for the administration of antimicrobials and for monitoring the patient and patient safety [expert consensus].

8. Infection control practitioners

Infection control practitioners play an essential role in the prevention of healthcare-associated infections, many of which are associated with inappropriate antimicrobial use, and as such can support the prudent use of antimicrobials through the provision of advice and peer review. Current evidence and expert opinion support the following as effective elements of guidelines to support and enable infection control practitioners in the control and prevention of antimicrobial resistance:

a. Ensure the collaboration of antimicrobial stewardship programmes and infection prevention and control activities by highlighting the role of appropriate antimicrobial use in the prevention and control of healthcare-associated infections [expert consensus].

9. Education / academics

Education and training are essential to the establishment of appropriate knowledge, attitudes and behaviour among healthcare professionals and the public. Current evidence and expert opinion support the following as effective elements of guidelines in respect of the role of education and academics in the control and prevention of antimicrobial resistance:

a. Ensure that all healthcare professionals are regularly trained on appropriate antimicrobial use [14,46]. Example: require participation in a minimum number of certified education activities on antimicrobial prescribing and use
b. Include training on prudent antimicrobial use in medical, nursing, pharmacy, dentistry and midwifery schools [expert consensus] [14,20]
c. Introduce education on prudent antimicrobial use, antimicrobial resistance, vaccination and hygiene in primary and secondary education. Example: through implementation of the e-Bug platform [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 their expectations, and the normative pressures that these can exert on peers and healthcare professionals, and their adherence to medication schedules. Current evidence and expert opinion support the following as effective elements of guidelines in respect of the public and patients in the control and prevention of antimicrobial resistance:

a. Get informed about appropriate antimicrobial use, antimicrobial resistance and adverse reactions to antimicrobials [expert consensus]
b. Do not use antimicrobials without a medical prescription [expert consensus]
c. Do not use leftover antimicrobials [expert consensus].

11. Research

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 and mitigate the risks of the development of resistance. Based on identified knowledge gaps, the following elements were considered important research targets to support the prudent use of antimicrobials:

a. Promote research that assesses and compares behavioural change interventions for antimicrobial prescribing, taking into account cultural differences, in order to improve our understanding of the optimal ways that rational antimicrobial prescribing practices can be achieved [47]
b. Promote research on interventional studies for antimicrobial prescribing [expert consensus]
c. Research the risk of specific antimicrobials and antimicrobial classes for the selection of antimicrobial resistance in microbiota to allow ranking and rational use [expert consensus]
d. Ensure that results from research on antimicrobials and antimicrobial prescribing are translated into practice [expert consensus]
e. Promote high quality clinical research studies on existing antimicrobials [expert consensus]
f. Promote research on rapid and point-of-care diagnostics to support evidence-based guidelines for the role of diagnostics in appropriate antimicrobial prescribing [expert consensus].

12. Pharmaceutical industry

The pharmaceutical industry is a key partner in efforts 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 the control and prevention of antimicrobial resistance:

a. Ensure that promotional activities are in accordance with the summaries of product characteristics (SPCs) and national guidelines, and that they mention the risks of antimicrobial resistance and inappropriate use [expert consensus]
b. Adapt pack size and strength to indications [14] [expert consensus]
c. Consider special labelling of antimicrobial packages that identify them as such and indicate that they are medical products for specific use only as prescribed [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, in the following domains: 1) international – organisations, agencies, 2) national and regional – governments, administrators, public health agencies, professional associations and scientific societies, 3) healthcare facilities, 4) laboratories, 5) prescribers, 6) pharmacists, 7) nurses, 8) infection control practitioners, 9) education/academics, 10) public and patients, 11) research and 12) the pharmaceutical industry.

Given the availability of evidence-based guidelines and systematic reviews, we 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 professional associations' websites. 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 [48,49]. In total, 39 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 [3,4,6,14,50]. 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 see 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 available relevant indicator lists, e.g. the DRIVE-AB project [35], the TATFAR structure and process indicators for antimicrobial stewardship programmes [51] and the ESAC-Net indicators on consumption of antibacterials [30]. 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.

An expert meeting on 9–10 June 2016 was organised by ECDC to solicit input and feedback from a panel of experts from Member States, selected on the basis of experience and research in the field of antimicrobial use both 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 of 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. This is the first draft of the guidelines and is open for public consultation until 5 September 2016.

A second meeting with European stakeholders, including professional societies, is planned for September 2016.

The draft guidelines are expected to be finalised and submitted to the European Commission by the end of October 2016.

Appendix 2. List of proposed examples of quantitative indicators

Proposed examples of indicators/metrics	Recommendation
Number of FTEs for antimicrobial stewardship activities	3b v.
Proportion of prescriptions compliant with guidelines	3b vii.
Proportion of antimicrobial treatment courses with documentation of indication in the notes among all antimicrobial treatment courses	3b viii.
Antimicrobial consumption measured in DDDs or DOTs per 100 patient-days (in healthcare facilities)	3b xiii.
Proportion of cases of *Staphylococcus aureus* bacteraemia where infectious disease consultation was provided	3b xiii.
Proportion of combination treatments among total number of antimicrobial treatments	5a v.
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)	5a ix.
Proportion of documented antimicrobial courses with reassessment after 48–72 hours	5a x.
Seasonal variation of the total antibiotic consumption (ATC code: J01) (in the community)	5b i.
Rate of compliance with administration of perioperative antimicrobial prophylaxis within 60 minutes before incision	5c ii.
Rate of compliance with discontinuation of perioperative antimicrobial prophylaxis within 24 hours after initiation of surgery	5c ii.
Incidence of *Clostridium difficile* infections	5c iv.

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