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White Paper: Bridging the gap between human and animal surveillance data, antibiotic policy and stewardship in the hospital sector—practical guidance from the JPIAMR ARCH and COMBACTE-MAGNET EPI-Net networks

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Background: Antimicrobial surveillance and antimicrobial stewardship (AMS) are essential pillars in the fight against antimicrobial resistance (AMR), but practical guidance on how surveillance data should be linked to AMS activities is lacking. This issue is particularly complex in the hospital setting due to structural heterogeneity of hospital facilities and services. The JPIAMR ARCH and COMBACTE-MAGNET EPI-Net networks have joined efforts to formulate a set of target actions for linking surveillance data with AMS activities.

Methods: A scoping review of the literature was carried out addressing research questions on three areas: (i) AMS leadership and accountability; (ii) antimicrobial usage and AMS; (iii) AMR and AMS. Consensus on the target actions was reached through a RAND-modified Delphi process involving over 40 experts in different fields from 18 countries.

Results: Evidence was retrieved from 51 documents. Initially 38 targets were proposed, differentiated as essential or desirable according to clinical relevance, feasibility and applicability to settings and resources. In the first consultation round, preliminary agreement was reached for 32 targets. Following a second consultation, 27 targets were approved, 11 were deleted and 4 were suggested for rephrasing, leading to a final approved list of 34 target actions in the form of a practical checklist.

Conclusions: This White Paper provides a pragmatic and flexible tool to guide the development of calibrated hospital-surveillance-based AMS interventions. The strength of this tool is that it is a comprehensive perspective that takes into account the hospital patient case-mix and the related epidemiology, which ultimately drives antimicrobial usage, and the feasibility in low-resource settings.

Introduction

Recommendations from major international public health institutions unanimously consider surveillance and antimicrobial stewardship (AMS) as fundamental pillars in the fight against antimicrobial resistance.[1–3] However, the different structures of healthcare systems around the globe and the non-homogeneous availability of surveillance data and resources make these activities difficult to standardize. Therefore, guidance on practical aspects is lacking for many of these activities. Promotion regarding the safe use of antibiotics, for example, is becoming a strictly regulated issue in a growing number of countries with mandatory implementation of AMS programmes within the 'quality and safety improvement' framework. However, national recommendations in high-resource settings have difficulties in precisely indicating which types of professional figures and the amount of time necessary to carry out these activities.[4] Similarly, many practical guidelines for the implementation of stewardship policies in acute care hospitals recommend tailoring AMS interventions to local epidemiology and needs, but rarely provide details on how surveillance data should intertwine with stewardship activities.[5–7] Only fragmentary indications are available concerning the type and frequency of data reporting, modalities for data aggregation and, more importantly, to what extent these data should inform AMS strategies, especially in terms of optimizing empirical prescribing.[6,8–10] Additionally, even if most of the available literature focuses on acute care hospitals, the complexity of the 'acute care' structure means that the few available recommendations are not always generalizable, especially when considering special settings, such as ICUs, emergency departments and paediatric and oncohaematology wards.

Another key issue that is relevant to practical implementation of AMS programmes is the importance of having appropriate measures of antimicrobial consumption. While a vast body of literature is available on the topic, more practical guidance on what should be implemented in various settings would be of use to stakeholders who want to establish AMS interventions.

The JPIAMR ARCH[11] and COMBACTE-MAGNET EPI-Net[12] networks have joined forces to design a framework that provides a set of actions to facilitate antibiotic policy interventions and drive the link between surveillance data on antimicrobial resistance (AMR) and consumption and implementation of AMS activities.

The ARCH and COMBACTE MAGNET EPI-Net international expert panel has produced a series of four White Papers—'Bridge the Gap: Survey to Treat'—that are specifically focused on four settings: hospital; outpatient; long-term care facilities (LTCFs); and veterinary. The actions identified in the four White Papers, developed in the form of practical checklists, summarize the epidemiological, microbiological and antimicrobial data that are essential for antibiotic prescribing and policy. Three research questions were developed that constitute the evidence base for the recommendations focused on three main areas: (i) AMS leadership and accountability; (ii) antimicrobial usage (AMU) and AMS; and (iii) AMR and AMS. The practical framework is intended to guide a process to combine surveillance reports of AMU and resistance rates with AMS policy interventions in hospital, outpatient, LTCF and veterinary settings.

The process of the elaboration of these papers was underpinned by the One Health approach and had a strong focus on the feasibility of the recommended actions and their practical applicability in heterogeneous economic settings that include low- and medium-income countries (LMICs) as well as in contexts with limited expertise in surveillance and AMS. The hospital setting is discussed in the present White Paper. The intended audience of this White Paper is health professionals, including those with limited experience with AMS interventions, operating in the hospital setting and planning to start an AMS programme at their facility. Dissemination to the intended audience will be ensured by the networks involved in the JPIAMR ARCH project as listed in Table 1. Checklist formats of the target actions for the four settings are available for download on the ARCH website.[11] These checklists can be used by health professionals and policymakers to establish and/or monitor stewardship activities.

Methods

Using a One Health approach, the process was underpinned by the development of expert consensus based on evaluation of the available literature and guidance documents on AMS and surveillance. This was followed by the development of a first draft of targets and a RAND-modified Delphi process for the definitive validation of targets (protocol available at the ARCH website[11]).

Over 40 experts from 18 countries and 30 networks in infectious diseases (IDs), clinical microbiology, AMS, veterinary medicine and public health developed the protocol, contributed to all phases of the consensus and approved the final recommendations. Tables 1 and 2, respectively, detail the networks and stakeholders involved. A conflict of interest form was signed by each participant before starting the consensus process. During development of the project, the experts were divided into four distinct working groups, each one focusing on a separate setting. Each group was led by two senior researchers with the task of evaluating the body of evidence retrieved and who participated in the process of drafting the first set of recommendations for each specific setting. Details of the process are outlined below.

1. Development of research questions

The protocol and an initial set of research questions were drafted by the entire group based on personal expertise and the results of the EPI-Net COACH systematic review of AMR surveillance. The EPI-Net COACH project was launched in 2018 and targeted modalities of AMR surveillance linked to AMS in order to provide guidance to tailor stewardship interventions.[13] The general set of research questions is reported in Table 3. Slight modifications of the original set of questions were made, as necessary, to adapt the review process to the four different settings.

Table 1. Networks involved

No.	Acronym	Network
1	ANISS	Austrian Network for Nosocomial Infection Surveillance System
2	AMCLI	Associazione Microbiologi Clinici Italiani
3	CAESAR	Central Asian and Eastern European Surveillance of Antimicrobial Resistance network
4	CERMEL	Centre de Recherches Médicales de Lambaréné
5	CDDEP	Center For Disease Dynamics, Economics & Policy
6	JPIAMR-CONNECT	inCreasing cOmmunicatioN, awareNEss and data sharing in a global approaCh against resisTance
7	DZIF CRU	German Centre for Infection Research (DZIF), Clinical Research Unit for healthcare associated infections
8	EUCIC	European Committee on Infection Control
9	EARS-NET	European Antimicrobial Resistance Surveillance Network
10	EARS-Vet	European Antimicrobial Resistance Surveillance network in Veterinary medicine
11	EUCAST	European Committee on Antimicrobial Susceptibility Testing
12	FIDSSA	Federation of Infectious Diseases Societies of Southern Africa
13	FASTEN	Fighting Antimicrobial Resistance with STewardship Education Network
14	GAP-ONE	Global Antimicrobial resistance Platform for ONE Burden Estimates
15	VGCARE: HANNET	Vietnamese German Center for Medical Research: Hanoi Network
16	HiGHmed	Heidelberg-Goettingen-Hannover Medical Informatics
17	IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
18	APUA	Alliance for the Prudent Use of Antibiotics
19	ISID	International Society for Infectious Diseases
20	ISAC	International Society of Antimicrobial Chemotherapy
21	IZSVe	Istituto Zooprofilattico Sperimentale delle Venezie
22	KISS	Krankenhaus-Infektions-Surveillance-System (German National Reference Center for Surveillance of Nosocomial Infections)
23	COMBACTE LAB-Net	Combatting Bacterial Resistance in Europe (COMBACTE), Laboratory Network
24	LOTTA NETWORK	Long-Term care facility TriAls Network
25	PENTA-ID	Paediatric European Network for the Treatment of AIDS and Infectious Diseases
26	REIPI	Red Española de Investigación en Patología Infecciosa (Spanish Network for Research in infectious diseases)
27	SAASP	South African Antibiotic Stewardship Programme
28	SIM	Società Italiana di Microbiologia
29	SIMPIOS	Società Italiana Multidisciplinare per la Prevenzione delle Infezioni nelle Organizzazioni Sanitarie
30	VetEffecT	Global specialists in Circular Animal Production, veterinary and public health

2. Narrative review of the evidence

A comprehensive literature search was carried out by seven reviewers (M.D.P., F.M., F.A., M.S., E.C., M.C. and L.G.) with the aim of identifying the existing evidence (clinical studies, guidelines and recommendations) relative to the use of data from microbiological surveillance and antibiotic consumption to inform AMS policies. For the literature search relevant articles in English, published in the last 10 years, were screened with a step-wise approach: first guidance (from scientific societies, international and national authorities) and documents included in the repository created by the EU-JAMRAI.[14] Secondly, a search using MEDLINE (National Library of Medicine, Bethesda, MD, USA) was carried out with a combination of the following terms: antimicrobial consumption, antimicrobial drug resistance and surveillance.

All potentially relevant publications were screened by a single reviewer and evaluated against protocol eligibility criteria based on title and abstract. Any uncertainties were resolved by a second reviewer after evaluation of the full-text article. The publications included were summarized qualitatively into three evidence tables where information on the year, author/organization issuing the publication and part of the text relevant to each research topic was reported.

A first draft of targets was formulated by the reviewers and leaders of each working group after evaluation of evidence extracted that addressed the initial set of research questions. Key questions for which poor-quality evidence or no evidence was retrieved were suggested as a topic for further research. Recommendations, state of the art and original approaches were evaluated by focusing on feasibility and adaptability to different economic and healthcare contexts to compile a list of 'essential' and 'desirable' targets. Targets were recognized as 'essential' when widely practicable if not already broadly accomplished, and 'desirable' in case of limited feasibility or if they had a resource-intensive nature.

3. Consensus process

Consensus on essential and desirable targets was reached by using a RAND-modified Delphi approach based on a web-based survey followed by discussion during a face-to-face meeting. In October 2019, prior to the face-to-face meeting, the expert panel received the summary of the

Table 2. EPI-Net description and correlated activities

EPI-Net activities	
Surveillance of resistant and healthcare-associated infections	Surveillance-dedicated website (epi-net.eu) conceptualized as a single platform integrating surveillance data from humans and animals in Europe providing: • up-to-date information on prevalence and incidence in antimicrobial resistance and healthcare-associated infections • outbreak data from published reports and surveillance systems
Central Data Repository for surveillance data	Bi-annual rounds of data collection from multiple sources (national/international, mandatory/voluntary surveillances) for a One Health database dedicated to European epidemiology data on prevalence and incidence of clinically relevant antimicrobial-resistant fungi and bacteria, incidence of HAI and outbreaks. The database also catalogues newly approved antibiotics.
Scientific activities	
• Implementation of frameworks for semi-automation of procedures for surveillance of HAIs. • Building networks of healthcare centres sharing epidemiological data to receive statistical model-supported individualized feedback on interventions to reduce setting-specific AMR rates. • Development of standardized decision-support models, capable of defining the thresholds in resistance data for various infectious disease syndromes and changing empirical antibiotic treatment protocols accordingly. • Analysis of burden and outcomes of infections due to multidrug resistant organisms.	

Table 3. Research questions

1. Leadership commitment, accountability and antimicrobial stewardship team
- Participants in the AMS team
- Institutional support for organization and management of AMS programmes: legal framework
- Institutional support for organization and management of AMS programmes: staffing personnel
2. Antimicrobial usage and antimicrobial stewardship
- Which antibiotics should be monitored?
- Which metrics should be employed for AMU monitoring?
- Who should receive the report from the AMS team?
- What time interval should be adopted for reporting?
- Which criteria should be used to define a ranking for antibiotic use?
3. Antimicrobial resistance surveillance and antimicrobial stewardship
- Which pathogens should be targeted?
- How should resistance be monitored?
- Should non-clinical samples (e.g. screening and colonization status) be monitored?
- What time interval should be adopted for reporting surveillance data?
- Which stratification criteria should be adopted?
- Should the report be delivered to healthcare professionals other than the AMS team?
- Should specific thresholds be set for driving AMS recommendations for empirical therapy?
- Should specific thresholds be established for driving AMS recommendations for medical and surgical prophylaxis?
- Which criteria should be used to drive selective reporting of antibiograms?

evidence and a first proposal of the targets addressing each of the preselected key questions. Using a SurveyMonkey questionnaire, participants were asked to express their agreement with the content of the targets and the level of recommendation on a nine-point Likert scale. Consensus on single targets was reached if the median score was higher than 8 with at least 70% of the experts scoring in the highest tertile (i.e. scores of 7, 8 or 9).

A 2 day face-to-face meeting was held at the end of October 2019 during which the experts were presented with a summary of the evidence relative to each setting and the results of the web-based survey. The entire set of recommendations was reviewed and discussed, and a final decision was made on whether to keep or retain recommendations that did not meet the predefined threshold for agreement. The content of the remaining targets could also be rephrased following the suggestions of the panel.

After the face-to-face meeting, a final list of targets was drafted and approved by the entire expert panel. Targets on which agreement was not reached because of unconvincing evidence were added as priority topics for further research.

Results

A total of 51 documents for evidence appraisal were evaluated.[1,4–8,10,15–57] The majority ($n = 39$, 76%) were from high-income countries. An initial set of 38 targets was proposed based on the available evidence. Twenty experts rated the targets via the online survey. Agreement was reached for 32 targets, of which 17 were labelled for editing due to new comments provided during the survey. The remaining six targets were kept for discussion. The majority of the comments were related to: the participants of the AMS team and staffing personnel; antibiotics to monitor and definition of prescription appropriateness; time interval for reporting; resistant pathogens to target in different hospital wards; MIC reporting; and report stratification criteria and report delivery.

During the face-to-face meeting (October 2019), 27 targets were approved, 11 were deleted and 4 suggested for rephrasing.

Table 4. Leadership commitment, accountability and antimicrobial stewardship team

Participants in the antimicrobial stewardship team
1.1. Essential All hospitals should establish a multidisciplinary antimicrobial stewardship team. The core members should always include an antibiotic prescriber and a pharmacist trained in infection management, antimicrobial usage and antimicrobial resistance or another professional with a similar role.
1.2. Desirable The antimicrobial stewardship team should have core members comprising an infectious disease specialist and/or a clinical microbiologist, and an infection control professional trained in antimicrobial usage and resistance.
1.3. Desirable Include additional figures in the core group according to the setting, resources and type of intervention (i.e. other specialists from target wards, infection control nurses, clinical psychologists and IT experts).
Institutional support for organization and management of antimicrobial stewardship programmes: legal framework
1.4. Essential Regulate and promote antimicrobial stewardship activities at every level of the healthcare organization with well-defined roles and responsibilities and a clear governance structure.
Institutional support for the organization and management of antimicrobial stewardship programmes: staffing personnel
1.5. Essential Include dedicated time and specific salary support for antimicrobial stewardship activities as part of antimicrobial stewardship programmes.
1.6. Essential Allocate full-time equivalents according to national requirements for the different settings and level of intervention, where available.

Following another round, the whole panel then approved a final list of 34 targets. Tables 4–6, respectively, list the recommended targets for the AMS team, AMU and AMS, and AMR and AMS.

For four research questions ('Which criteria should be used to drive selective reporting of antibiograms?'; 'Should specific thresholds be established for driving AMS recommendations for medical and surgical prophylaxis?'; 'Should specific thresholds be set for driving AMS recommendations for empirical therapy?'; and 'Which criteria should be used to drive selective reporting of antibiograms?'), the summary of evidence did not allow formulation of specific targets, and thus these topics were addressed as future research areas (Table 7).

Discussion

Based on review of the available evidence, followed by expert consensus, a list of essential and desirable actions was provided that cover the three main core components of the stewardship framework: structural organization (participants, legal framework and staffing personnel), surveillance (monitoring of both AMU and AMR to identify potential targets for interventions) and reporting. With regard to structural organization, the AMS team should be multidisciplinary and work with the full support of hospital administration. The composition of teams should depend on the size of the hospital and availability of resources. Considering that in most LMICs having an ID specialist or a clinical microbiologist to head the team is not possible, it is essential to have GPs who are properly trained in infection management and antimicrobial use or who are already sufficiently experienced to lead AMS activities.[8,10,18,20,34] Where resources allow it, core members should belong to the ID/microbiology areas with the essential contribution of a senior pharmacist with a specific expertise in antimicrobials; additional members can include an infection control practitioner, nurse, member of the IT department and/or a programme manager and specialists from other departments for programmes aimed at covering areas of particular complexity or different prescribing patterns (i.e. ICUs, haemato-oncology wards, emergency departments and paediatrics).

Within the AMS committee, the hospital Chief Executive Officer (CEO) or a member of the executive and the leader of the AMS programme team should work together with several other professionals to promote AMS interventions and link them with surveillance and infection prevention and control activities. Feedback on these activities should always be presented and discussed among hospital leadership. Planning dedicated time for AMS activities is essential. Because many determinants influence the need for human resources (i.e. the institutional structure and size, setting where the intervention is carried out and stages of the intervention itself), it is difficult to standardize the total amount of full-time equivalents (FTEs) per number of hospital beds. FTEs should be divided among the essential core elements of the team and allocated according to national requirements.[10,15,16,19,49]

Only a limited number of guidance documents have clearly stated which antibiotics should be routinely monitored. It is essential to monitor high-volume or top-ranking (i.e. most used) agents to capture significant variations and shifts in use and to relate data to local antimicrobial resistance trends. When possible, total consumption for antibiotics for systemic use (ATC J01 class) should be reported and further stratified by antibiotic classes (J01 subgroup) or individual agents.[15,21,22,40,48] Data stratification according to the new AWARE index, introduced by the WHO in the Essential Medicines List,[37] is an alternative to promote benchmarking.[45,53]

Table 5. Antimicrobial usage and antimicrobial stewardship

Which antibiotics should be monitored?
2.1. Essential Monitor: - overall consumption of antibiotics - IV and oral antibiotics used in high volumes or according to the local ranking (5–10 most-used agents) - antimicrobials included in the Watch and Reserve categories (WHO Essential Drug List AWARE index) - antibiotics used for treating infections caused by local clinically relevant resistant pathogens as defined by the antimicrobial stewardship team
2.2. Essential Monitor agents or antimicrobial classes included in the antimicrobial use surveillance programme or antimicrobial stewardship plan in countries or regions that developed specific plans for antimicrobial stewardship and antibiotic use surveillance.
2.3. Essential Monitor the antibiotics that are targets of stewardship interventions in your setting and their plausible alternatives.
2.4. Desirable Monitor the total consumption of systemic antimicrobials (ATC J01 class), both intravenous and oral formulations, as overall aggregated data and as subclasses (J01A, J01B, J01D, J01E, J01F, J01G, J01M, J01X) or individual agents.
2.5. Desirable Monitor all antibiotics used in the hospital.
2.6. Desirable Monitor antibiotics used for medical and surgical prophylaxis.
2.7. Desirable Monitor systemic antifungal agents (agents included in the ATC J02 group) if the antimicrobial stewardship intervention is targeting institutions/wards with high rates of invasive fungal infections (i.e. haematology, transplant centre, ward with high consumption of broad-spectrum antibiotics).
Which metrics should be employed?
2.8. Essential In high-resource settings, monitor DDD and/or DOT in the adult population and DOT in the paediatric population by defined denominators. Define denominators and source of data in the report.
2.9. Essential When DDD/DOT monitoring is not feasible, perform at least an annual point prevalence survey, providing data on prevalence of antimicrobial use in each hospital ward, along with main indications for prescription and eventually appropriateness evaluation, for regular surveillance and for baseline assessment informing ASP design and implementation.
2.10. Desirable Stratify antimicrobial usage data according to WHO AWaRe index categories to evaluate usage shift and reduction of usage of reserve and watch antibiotics.
2.11. Desirable Supplement antimicrobial usage data with assessments of appropriateness of therapy (e.g. documentation of antimicrobial indication, compliance with local formulary and guidelines, duration and timing of surgical prophylaxis).
Report delivery
2.12. Essential Deliver performance reports to prescribers, nurses, hospital executives/medical leadership and services cooperating with the antimicrobial stewardship team (microbiology, Infection Prevention and Control team, drugs therapeutic committee and other relevant staff).
2.13. Desirable When a web platform for antimicrobial usage reporting is in place, set up a section dedicated to the role of surveillance and stewardship for the general public.
Which time interval for reporting?
2.14. Essential Provide antimicrobial consumption data on a regular basis, at least annually, depending on the size of the institution and quantity of prescribed antibiotics.
2.15. Desirable Where resources allow, provide antimicrobial usage reporting more frequently than yearly (e.g. quarterly/twice yearly).

Table 6. Antimicrobial resistance surveillance and antimicrobial stewardship

Which resistant pathogens should be targeted?
3.1. Essential Monitor methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, carbapenem-resistant Gram-negatives, ESBL-producing bacteria and colistin-resistant Gram-negative bacteria in all blood cultures and *Clostridioides difficile*.
3.2. Essential In highly endemic settings for tuberculosis, check availability of local data on resistance in tuberculosis and consider having a section of the periodic report summarizing the most important information.
3.3. Essential Before starting a surveillance programme, ensure minimum infrastructural requirements and alignment with quality control programmes to support AMR surveillance.
3.4. Essential Monitor antibiotic resistance to new antibiotics in settings highly endemic for multidrug-resistant Gram negatives.
3.5. Desirable Monitor resistance in *Candida* spp. if the stewardship intervention is targeting institutions/wards with high rates of invasive fungal infections (i.e. haematology, transplant centre, ward with high consumption of broad-spectrum antibiotics).
How should resistance be monitored?
3.6. Desirable Monitor MICs (or inhibition zones) of resistant bacteria of primary clinical importance at the local/unit level.
3.7. Desirable Where resources allow, monitor molecular mechanisms of resistance in clinically relevant strains according to the antimicrobial stewardship team.
Should non-clinical samples (screening and colonization status) be monitored?
3.8. Desirable Monitor resistance in screening samples in settings with infection control measures applied to colonized patients (e.g. targeting screening and contact precautions, preventive isolation).
Which time interval should be used for reporting?
3.9. Essential Provide an annual analysis of cumulative susceptibility data on the identified resistant bacteria target at your facility.
3.10. Desirable Where resources allow provide antimicrobial resistance reporting more frequently than yearly in certain settings and/or for specific endemic resistant phenotypes (ICUs).
Which stratification criteria should be adopted?
3.11. Essential Provide unit-specific resistance surveillance data.
3.12. Desirable For settings where the number of infections per genus is limited (i.e. neonatal or paediatric intensive care units), check if regional data (for the same setting) are available and evaluate if generalizability of the data to your setting is applicable.
Report delivery
3.13. Essential Deliver a report to prescribers with a commentary; consider highlighting specific data that might require re-evaluation of therapeutic guidelines.

Approaches that are more specific can be considered in the case of predefined outcome measures addressing specific syndromes and/or settings (i.e. anti-MRSA drugs or antibiotics that carry a high risk of precipitating *Clostridioides difficile* infection).

Adoption of DDD and/or days of therapy (DOT) divided by a standardized denominator is recommended. In the paediatric setting, due to high variability in body weight, DOT is preferred. It was considered probable that two metrics would need to be used simultaneously as per previous guidance,[58] but this option has limited applicability in LMICs as it represents an extra workload. Types of denominators [100(0) patient days (PD)/day present (DP)/occupied bed days (OBD)], data sources (purchased/dispensed/

Table 7. Research priorities

• **Define thresholds to direct therapy decisions** **Rationale** There is no evidence to guide precise assessment definition of thresholds at which empirical therapy suggested in the hospital formulary and/or by the antimicrobial stewardship team should be changed. In addition to local resistance rates, important aspects to consider when deciding on antimicrobial therapy are the patient's risk factors, severity of infection, access to antibiotics (which depends on the country) and setting (not only hospital versus community, but also different hospital wards). Considering that there is no solid evidence for a real threshold to adopt, the use of risk factors, severity of infection, setting and a patient-centred approach is the most reasonable strategy to direct therapy decisions and should be further explored.
• **Establish criteria for ranking antibiotics** **Rationale** A 'ranking of antibiotics' based on their ecological impact, PK/PD properties and toxicity can be a valuable tool to inform restrictive AMS intervention or to guide de-escalation. Selective reporting is a useful tool to drive the appropriate use of antimicrobial agents, but no criteria on which antibiotics should be concealed have been clearly defined. Studies on innovative strategies to identify standards for antibiotic classification and ranking for antimicrobial stewardship should be performed.
• **Develop stewardship guidelines for specific sub-settings** **Rationale** The available evidence in this field is not sufficient to provide recommendations by settings. Further research is needed to develop stewardship interventions adapted and validated for high-risk patients, specifically paediatrics and the immunocompromised.

administered data) and providers need to be clearly specified as they can generate relevant variations in metrics. Point prevalence surveys on antibiotic use, in both adult and paediatric inpatients, can provide useful information to detect problematic areas needing prompt AMS interventions or in the case of unavailability of AMU density data. As for the frequency of reporting, reporting of data yearly is recommended, although more frequent intervals can be considered.[10,15,22] The panel agreed that it is essential to share AMU data with all prescribers, hospital medical leadership/executives and other disciplines involved in AMS activities.[1,6,15,20,26]

One of the major goals of AMS is to improve prescription appropriateness. Different criteria have been used to assess appropriateness: definitions based on *in vitro* susceptibility (which are limited to cases with positive cultures); expert opinion based (which are subjective); compliance with local guidelines; or a combination of these criteria.[59] The expert panel held that assessment of appropriateness of prescriptions is essential. However, objective criteria to measure it have yet to be determined in terms of individual prescriptions and facility-level consumption.

Selection of target bacteria should be based on local/national epidemiology and on the major clinical impact attributable to a specific patterns of bacterial resistance. In special settings (i.e. immunocompromised patients or ICUs), opportunistic resistant pathogens responsible for major clinical syndromes should also be monitored. Monitoring of *C. difficile* was considered to be an essential indicator of AMU at the patient level. An essential requirement of reporting is to allow distinction between clinical and screening/colonization samples. Therefore, blood cultures should be preferred instead of other specimen types due to their high level of sensitivity. In settings where other clinical samples might play a role (i.e. broncho-alveolar lavage in the ICU as a proxy for ventilator-associated pneumonia aetiology), they can also be reported as distinct numbers. Reporting of screening samples was more debated; the panel recommends careful interpretation of these data and suggests reporting to the AMS team if specific antibiotic policies are in place (i.e. surgical prophylaxis in MRSA-positive patients).

Resistance data should be displayed using cumulative stratified antibiograms, making sure to adopt adequate de-duplication strategies and to separate clinical from screening samples.[13] Either qualitative interpretative categories or MICs can be used to express susceptibility/resistance results; the choice between them needs to account for the final recipients and the purpose of the report. Nevertheless, monitoring of MIC distributions is important to identify WT phenotypes, aid clinical decisions on treatment and compare testing of new agents. Among the antimicrobial susceptibility testing (AST) methods, broth dilution tests are considered the gold standard for MIC determination; they are standardized by different organizations[60–62] and should be used whenever possible. However, they are time-consuming to perform, require certain knowledge (are influenced by the reader, incubation time, temperature and inoculum size) and do not provide insights on resistance mechanisms.

If broth dilution tests are not available, well-standardized alternatives include gradient methods (i.e. Etest) and disc diffusion tests, with the shortcoming of potential biases towards higher or lower MICs determined by the Etest and of qualitative results provided by the diffusion techniques.[63,64] Automated systems and genotypic test methods are relevant for epidemiological analysis as they can detect resistance genes or their products, thus helping to guide treatment protocols, but they are not technically feasible for all laboratories. In such circumstances, it is suggested that a reference laboratory be identified for technical support (Table 8

Table 8. Main advantages and limitations of molecular (DMM) and conventional (CA) diagnostic techniques in antibiotic-resistance

Core element	Molecular methodology	Conventional antibiogram	DMM	CA
Time frame	• 3 h maximum (5–6 h longer from blood culture) • Appropriateness of antibiotic prescribing (except in critical patients) • Immediate change from empirical therapy to targeted therapy	• 16–24 h	▲	▼
Sample	• Directly from clinical sample or blood culture positive	• From bacterial culture	▲	▼
Microbiology characteristic	• Only some molecular methods distinguish homogeneous and heterogeneous bacterial populations • No bacterial load • No morphology from bacteria colonies • VBNC identification (viable bacteria but not culturable) • Useful for microorganisms that are difficult to cultivate or that have long growth times (mycobacteria, clostridia, *Helicobacter*)	• Homogeneous and heterogeneous bacterial population • Load and living bacteria • Morphology of bacterial colonies	■	▲
Gene expression	• Identification of resistance genes that are not expressed owing to silencers or repressors • No identification of gene expression	• Yes	■	▼
Breakpoint indicator	• No	• Yes, MICs and ECOFF value	▼	▲
Species-specific identification and antibiotic resistance	• Simultaneous species-specific identification, multidrug resistance and genotyping	• Yes	▲	▲
Target resistance	• Intrinsically unable to detect unknown resistance mechanisms • Narrow repertoire of detectable resistance mechanisms covered by the available systems	• Multiple targets (coverage of all unknown and known resistance mechanisms)	▼	▲
Genotyping	• To know molecular local epidemiology of community and healthcare-associated infections. • Genomic comparison between humans/human and animal/human infection or colonization (livestock-associated infection). • Additional information for AMS	• NA	▲	▼
Costs	• Expensive	• Less expensive than molecular methodology	▼	▲

▲, advantage; ▼, limitation; ■, support technique; NA, not applicable.

lists the advantages and disadvantages of traditional AST and molecular methods).

There was general agreement on the need for at least annual reporting of antimicrobial resistance data, and twice-yearly reporting can also be considered.[8,15,18,27,29,30] Stratification of the results needs to be performed by unit, since hospital-wide antibiograms can mask trends in specific units.[8,10,15,27,30,56] In reporting the prevalence of resistance, a denominator of <30 isolates of a particular species is discouraged.[18,60,65] Where local antibiograms are not available, use of regional resistance data[28] should be considered. Similar to the AMU report, AMR results should be delivered to the facility's prescribers with comments to promote understanding and engagement.[1,28] Of note, the report should also integrate infection and prevention control measures, if in place. It was also suggested that an English language version of the report be formulated to promote dissemination of data between countries.

At present, there are insufficient data to recommend thresholds for establishing empirical therapy and prophylaxis. However, indications are available for management of hospital-acquired pneumonia, ventilator-associated pneumonia and urinary tract infections.[42,44,46,55] Other relevant areas identified among the priorities for future research are the development of specific criteria to guide decision-making regarding promotion and/or restriction of certain agents and the development of stewardship guidelines for the 'high-risk patient' category.

Intrinsic limitations of our work include the subjective nature of the experts' opinions, the narrative nature of the review and the main focus on bacterial infections. Finally, the experts discussed the need to extend or draft similar consensus targets for tuberculosis and other pathogens (fungi and viruses) in the future.

Conclusions

Many of the current guidance documents purposely include generic recommendations to allow greater flexibility by the end user according to the characteristics of individual sites. A major strength of this work is, in fact, the categorization of recommendations, where essential targets refer to what are considered the minimum requirements that need to be in place. Furthermore, the requirements were prioritized and developed taking into account settings with budgetary constraints, which often lack adequate capacity and support (in terms of qualified personnel and laboratory infrastructure). Another value of this White Paper is the attempt to differentiate the actions between different hospital wards (i.e. paediatric versus ICU versus haemato-oncology) considering differences in local epidemiology and patient characteristics.

This consensus provides a checklist of what should be considered the cornerstones of a hospital AMS programme that can be easily implemented at every level of healthcare and be modelled according to the heterogeneous economic settings. It also highlights specific areas lacking specific guidance, which should be the targets for future research and investment.

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