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ANTIMICROBIAL STEWARDSHIP PROGRAMME OUTCOMES IN A SECONDARY CARE HOSPITAL

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Abstract

Antimicrobial stewardship programmes (ASPs) are now expected in hospitals of every size, yet much of the evidence behind them comes from large teaching centres. This narrative review summarises what published studies show about ASP outcomes and what that implies for secondary care hospitals, which have fewer specialists and smaller laboratories. It covers intervention types, how outcomes are measured, effects on antibiotic use, clinical and microbiological results, costs, and implementation barriers. Consumption falls and prescribing quality improves reasonably consistently, with no signal of harm, while effects on resistance are less certain. The review reports no new data. Study designs are often weak, and metrics differ.

1. INTRODUCTION

Antibiotics are among the most frequently prescribed drugs in hospital. Point prevalence surveys in US and European acute care hospitals found that roughly a third to a half of inpatients were receiving an antimicrobial on the survey day, with a good share of the prescriptions for indications where the benefit was doubtful [1, 2]. Audits of inpatient antimicrobial use have long found that a substantial portion is unnecessary or inappropriate in drug choice, dose or duration [3, 4]. Every unnecessary day of treatment adds to selection pressure for resistant organisms, which in turn raises the burden of infections that are harder and more costly to treat [5, 6].

The scale of that burden is increasingly well documented. Resistance also carries a considerable economic cost through longer stays, costlier drugs and lost productivity,

although published estimates differ widely in method and are uncertain [7]. Reviews of the global picture describe resistance as a multifaceted problem that is already causing substantial illness and death, with the heaviest burden in low-resource settings [8]. Individual patient studies add detail. Bloodstream infection with methicillin-resistant Staphylococcus aureus, for instance, was linked to higher mortality, longer stay and greater cost than infection with susceptible strains [9]. These figures set the case for action, though they say little about which action works.

Antimicrobial stewardship is the organised effort to ensure that patients receive an antimicrobial only when needed, in the right drug, dose, route and duration. The Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America issued a joint policy statement on institutional programmes in 2012 with the Pediatric Infectious Diseases Society, and the first two societies published full guidelines in 2016, and the US Centers for Disease Control and Prevention set out core elements that hospitals of any size could adopt [10, 11, 12]. The World Health Organization has produced a practical toolkit for stewardship in low- and middle-income countries [13]. Programmes are therefore widely recommended, which makes the quality of the evidence for their outcomes a fair question.

This review looks at that evidence with secondary care hospitals in mind, meaning district or general hospitals without a full range of subspecialties, usually with limited infectious diseases, microbiology and pharmacy staffing. It is a narrative synthesis of published systematic reviews, trials, quasi-experimental studies and guidance, and it reports no data from any one hospital and no new analysis. Reported findings are collected in table 1, and the spread of those entries by outcome domain is shown in fig. 1. Because published ASP studies vary greatly in design and in the measures they use, special attention is paid to how outcomes were defined and how far each conclusion can be trusted [14, 15, 16].

A note on terms may avoid confusion. Stewardship, antibiotic stewardship and antimicrobial stewardship are used almost interchangeably in the literature, although the last also covers antifungal and antiviral drugs. Consumption is usually expressed as defined daily doses (DDD) per 1000 patient-days, or as days of therapy (DOT), which is less affected by dosing differences. Appropriateness has been assessed by explicit criteria and by expert panels, and the choice affects the numbers reported. Readers comparing studies should check which definitions were used before comparing percentages [17, 18]. Some programmes also report the proportion of prescriptions that were reviewed, which describes workload and reach but not effect, and should not be mistaken for an outcome measure.

Table 1: Reported outcomes of hospital antimicrobial stewardship interventions in published studies

Intervention or review	Reported finding	Ref.
Cochrane review of inpatient interventions	Better policy compliance and treatment about two days shorter, with no rise in mortality	[14]
Procalcitonin guidance respiratory infection	Lower antibiotic exposure in trial and pooled analyses without evident harm	[19, 20]
Post-prescription review and feedback	Feasible across hospitals; effect on use varied between sites	[21, 22]
Early oral switch medical wards	No worse outcomes and shorter hospital stay	[23]
Guideline-adherent empirical therapy	Associated with lower mortality in pooled studies	[24]
Rapid identification plus team review	Faster effective therapy in bloodstream infection; lower mortality and cost	[25]
Programme meta-analysis	Reduced use and cost with no signal of patient harm	[26]
Stewardship and C. difficile	Lower incidence, especially with restrictive programmes	[27, 28]
Stewardship with infection control	Fewer infections and colonisation with resistant bacteria	[28, 29]
Systematic review of value	Lower antimicrobial spending, inconsistent economic methods	[30]
Essential resources statement	Protected time and data access needed for programmes to last	[31]

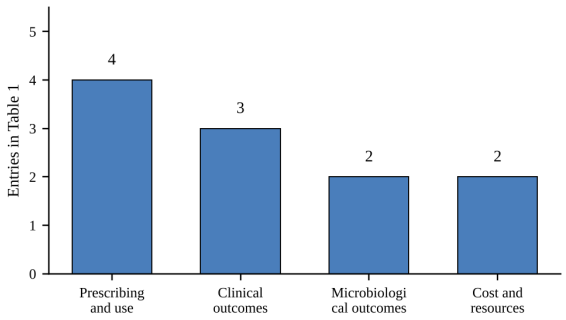


Fig. 1: Number of entries in table 1 by outcome domain

2. TYPES OF STEWARDSHIP INTERVENTION

Stewardship interventions are conventionally divided into persuasive and restrictive strategies, with structural supports underpinning both. Persuasive interventions include education, guidelines and local formularies, reminders, and feedback to prescribers. Restrictive ones include formulary restriction and pre-authorisation of selected agents. A Cochrane review of interventions to improve antibiotic prescribing for hospital inpatients concluded that interventions increased compliance with antibiotic policy and reduced the duration of treatment by about two days, without any increase in mortality, and that restrictive and enabling strategies both worked [14]. Hulscher and Prins reached a broadly similar view, noting that results in hospital practice are encouraging but depend on the context [16].

Prospective audit with feedback, sometimes called handshake stewardship, is probably the most widely used active strategy. A pharmacist or physician reviews antimicrobial prescriptions after they have been started, usually at 48 to 72 hours, and advises the prescriber if a change is indicated. Cosgrove and colleagues described a multicentre intervention of post-prescription review and feedback and found it feasible across several hospitals, with effects on antimicrobial use that varied by site [21]. Mehta and colleagues compared pre-authorisation with prospective audit and feedback and found that each approach could limit use, with differences in timing and in prescriber acceptance [22]. The two are complementary, and many programmes use both, restricting a few broad-spectrum agents and auditing the rest [11, 32].

Clinical decision support and diagnostic stewardship form a third group. Biomarker-guided therapy has been tested most widely for respiratory tract infection. In the ProHOSP randomised trial, procalcitonin-based guidelines reduced antibiotic exposure in lower respiratory tract infections without apparent harm [19]. A Cochrane meta-analysis of procalcitonin in acute respiratory infection later reported lower antibiotic consumption and, in the pooled data, a lower 30-day mortality [20]. Rapid diagnostics link to stewardship in a similar way. Huang and colleagues found that rapid organism identification by mass spectrometry, combined with stewardship team review, shortened time to effective therapy in bloodstream infection, and was associated with lower mortality and cost [25].

Several specific interventions targeted at common prescribing patterns have supporting evidence. Early intravenous-to-oral switch for patients who are improving and absorbing drugs was studied by Mertz and colleagues, who found no worsening of outcomes with early switching on medical wards and a shorter hospital stay [23]. Shorter fixed courses for infections such as community-acquired pneumonia and urinary tract infection have gained support, and Spellberg summarised the case that shorter is generally better, as long as the infection is uncomplicated and the patient responds [33]. Review of penicillin allergy labels is a further target, since most patients carrying the label tolerate penicillins on testing, and the label drives use of broader, more toxic alternatives [34, 35].

Structural elements make these interventions possible. The CDC core elements list leadership commitment, accountability, drug expertise, action, tracking, reporting and education [12]. A consensus exercise for global hospital programmes produced a related checklist that can be applied where resources are limited [36]. The 2018 statement on essential resources emphasised dedicated time for physician and pharmacist leaders and access to data, noting that programmes without protected time often

falter [31]. Within secondary care hospitals the structural elements are commonly the weakest link, because stewardship duties are added to existing posts. Evaluations of outcomes should therefore record the resources behind an intervention, not only its design [10, 31].

Team composition has received less attention than the interventions themselves, yet it shapes what can be delivered. Carling and colleagues credited their long-running programme to a multidisciplinary group in which physicians, pharmacists and microbiology staff shared responsibility, with authority to review and advise on targeted agents [37]. The 2012 policy statement had already proposed a core team of an infectious diseases physician and a clinical pharmacist with training in the field, supported by microbiologists, information specialists and infection control practitioners [10]. In a district hospital such a team may exist only on paper, with each member contributing a few hours. That can still work if roles are explicit, meetings are brief and regular, and one person owns the agenda and the follow-up of decisions [12, 31].

3. MEASURING STEWARDSHIP OUTCOMES

Outcome measurement in stewardship is harder than it looks. Ibrahim and Polk described the methodology of antimicrobial use metrics and the problems of benchmarking between hospitals, with differences in case mix, DDD definitions and data sources making comparisons unreliable [17]. DDD are fixed by an external body and do not reflect the doses patients actually receive, so a hospital that uses lower doses or renally adjusted regimens appears to consume less. Days of therapy count each drug administered per day, which is more intuitive for prescribers, but it counts combination therapy twice. Neither metric captures appropriateness, so a fall in use could reflect better prescribing or simply sicker patients being under-treated [16, 17].

Process and quality indicators address appropriateness more directly. Van den Bosch and colleagues carried out a consensus process to select indicators for appropriate antibiotic use in hospitalised adults, including documentation of indication, a timed review of therapy, timely switch to oral treatment and adjustment according to culture results [18]. Such indicators are practical for smaller hospitals, since they can be audited by hand on a sample of charts and do not need complex software. They also provide immediate feedback to prescribers. The limitation is that appropriateness judgements involve a degree of subjectivity, and inter-rater reliability needs checking when audits are done by different reviewers or at different times [15, 18].

Clinical outcomes are the most important endpoints and the hardest to attribute. Mortality, length of stay, readmission and treatment failure are all affected by many factors other than stewardship, and stewardship interventions usually change prescribing in only a subset of patients. Schuts and colleagues reviewed the evidence for objectives such as appropriate empirical therapy, de-escalation and switching, and found that those objectives were associated with improved outcomes where they could be measured [24]. A consensus group on research design stressed that studies should specify clear outcomes, adjust for time trends and, where possible, report balancing measures such as readmissions or deaths, so that benefits are not obtained at the cost of safety [15, 28].

Microbiological outcomes require longer time frames and larger populations. Changes in resistance rates among hospital isolates reflect many influences, including admissions from the community, antibiotic use outside the hospital and infection control. Baur and colleagues, in a large meta-analysis, found that stewardship was associated with reductions in infection and colonisation with several resistant bacteria and with Clostridioides difficile infection, with larger effects when stewardship was combined with infection control measures such as hand hygiene [28]. Lawes and colleagues, using time-series methods, linked a national stewardship and infection control strategy in Scotland to reductions in MRSA and C. difficile [29]. Smaller hospitals may lack the volume to detect resistance trends on their

own [28, 29].

Economic outcomes tend to be reported more optimistically than they are demonstrated. Drug acquisition costs are easy to measure, and many programmes show savings in this domain. Savings from shorter stays, fewer adverse events and avoided resistant infections are harder to establish, and few studies model them transparently. A systematic review of the value of hospital programmes concluded that programmes were generally associated with reduced expenditure on antimicrobials and often with improved clinical measures, but that economic evaluations used inconsistent methods [30]. A meta-analysis of clinical and economic outcomes similarly noted that benefits were consistent in direction, although the studies were heterogeneous, so pooled estimates should be read with caution [26, 32].

Study design determines how far an outcome can be believed. Uncontrolled before-and-after studies compare a period with the programme against one without, and any change in case mix, seasonal infection pattern or laboratory practice can masquerade as an effect. Interrupted time-series analysis improves matters by modelling the pre-intervention trend, and controlled designs add a comparison group that did not receive the intervention. The multinational group that proposed research recommendations urged investigators to choose such designs, to report all prespecified outcomes and to describe the intervention in enough detail to be reproduced [15]. Reviews of the hospital evidence base, including that by Hulscher and Prins, point to variable study quality, which tempers confidence in the larger effect sizes reported in the earlier literature [16, 32].

4. EFFECTS ON ANTIMICROBIAL USE, INFECTION AND PATIENT OUTCOMES

The most consistent finding across the literature is a reduction in antimicrobial consumption. Systematic reviews of inpatient programmes report reductions in overall use and in the use of targeted broad-spectrum agents, with the size of the effect varying with the intervention and baseline practice [14, 26, 32]. Carling and colleagues, who followed a multidisciplinary programme in a single hospital for seven years, described sustained reductions in targeted agents and favourable changes in susceptibility patterns [37]. Findings from single-centre before-and-after studies like this one should be treated as hypothesis-generating, since secular trends and concurrent changes in practice are difficult to exclude. They remain valuable because they show what is achievable over the long term in a specific setting [15, 37].

Evidence on patient-level outcomes is reassuring about safety. In the Cochrane review, hospital interventions that reduced antibiotic duration did not increase mortality, and some analyses showed a trend towards lower mortality [14]. Schuts and colleagues found that adherence to guideline-based empirical therapy was associated with lower mortality, and that switching from intravenous to oral therapy and de-escalation did not worsen outcomes [24]. Karanika and colleagues pooled studies of stewardship programmes and reported reduced consumption and costs, with no signal of harm to patients and, in some analyses, shorter stay [26]. The pattern is therefore that stewardship usually saves drugs without costing lives, which is important for clinician buy-in [14, 24, 26].

Effects on Clostridioides difficile infection are among the best documented. Feazel and colleagues pooled studies of stewardship programmes and found a reduction in incidence, especially for restrictive programmes, which is in keeping with the central role of broad-spectrum antibiotic exposure in the disease [27]. The result matters because C. difficile is a major cause of hospital-acquired diarrhoea and a frequent reason for prolonged stay. Baur and colleagues confirmed the finding in a larger analysis [28]. In secondary care hospitals with limited isolation capacity, reducing a preventable infection such as this yields a visible, tangible gain that staff understand, and that can be reported to managers without complex modelling [27, 28].

Effects on resistance are less clear cut. Reductions in resistant Gram-negative organisms and MRSA have been reported,

particularly when stewardship was paired with infection control [28, 29]. On the other hand, many individual hospital programmes see little change in resistance rates in the short term, and in the absence of a control group one cannot attribute changes to stewardship. Spellberg and colleagues warned in 2004 that the supply of new antibiotics was dwindling, which raised the stakes for preserving existing drugs [6]. Reviews of the causes and drivers of resistance argue that hospital efforts must be accompanied by action in the community and the animal sector if resistance is to be contained, which places the hospital programme in perspective [5, 38].

Persuasive and restrictive approaches differ in how quickly they act and how long the effect lasts. Restrictive measures such as pre-authorisation typically produce an early drop in use of the targeted drug, and the Cochrane review found that they changed prescribing faster than persuasive methods, though the gap narrowed over longer follow-up [14]. Pre-authorisation can, however, delay first doses, may shift prescribing to unrestricted alternatives and often provokes friction with prescribers [22]. Restrictive programmes appeared particularly effective against C. difficile in pooled analyses, perhaps because they limit exposure to the highest-risk drug classes [27, 32]. Persuasive approaches act more slowly but keep clinicians engaged, and a mixed model is therefore the usual compromise [14, 22].

5. IMPLEMENTATION IN SECONDARY CARE HOSPITALS

Smaller hospitals face recognisable constraints. Few have a full-time infectious diseases physician, microbiology services may be shared with a regional laboratory, and pharmacists carry heavy dispensing and ward duties. The Society guidance on essential resources acknowledges this and proposes scaled models in which a part-time physician or pharmacist leads, with remote support from a larger centre where needed [31]. The CDC core elements were designed with such hospitals in mind, and an ASP that implements leadership support, a named lead, one or two high-yield interventions and basic tracking can claim to meet them [11, 12]. Starting small and expanding with demonstrated success is the approach most consistently recommended [12, 31].

Choosing the first interventions is a practical decision. Common choices in smaller hospitals include a locally adapted empirical guideline for common syndromes, a timeout at 48 to 72 hours, restriction of a handful of broad-spectrum agents, and automatic stop dates for surgical prophylaxis. These require little technology and build on existing systems, and each has some evidence of effect [10, 12, 14]. Auditing a ward or two each month and feeding back results to prescribers can be done by a single trained pharmacist in a few hours. Local audit data also help to prioritise, because the commonest problems differ between hospitals, with respiratory infection, urinary infection and surgical prophylaxis featuring often in published audits [3, 4].

Information systems and diagnostics are frequent limiting factors. Without electronic prescribing, extraction of DDD or DOT data requires manual collation from pharmacy records, which is laborious but possible at a modest scale. Laboratory capacity influences how quickly culture results return and whether cumulative susceptibility reports (antibiograms) are produced. An antibiogram, updated annually and tailored to the hospital, is among the lowest-cost tools available and underpins the local empirical guideline [11, 12]. Where laboratory support is poor, as in many low- and middle-income settings, reviews of stewardship in Africa and elsewhere recommend focusing on feasible actions such as syndromic guidelines and surveillance of a small number of key pathogens [39, 40].

Culture and leadership shape success as much as structure. Prescribers in smaller hospitals often work alone or in small groups and may see feedback as a threat to autonomy. Published experience suggests that success is more likely when the programme is framed as support, when senior clinicians endorse it publicly and when the advice offered is practical and respectful of local conditions [10, 16]. Cox and colleagues, writing about low- and middle-income countries, observed that stewardship principles are the same everywhere but that barriers and priorities

differ, and that programmes need to be designed to local realities [40]. Involving nursing staff, who often influence cultures of prescribing and administration, is helpful but is seldom reported formally [11, 39].

Sustainability is the final test. Many early gains in consumption erode when the champion leaves or attention shifts. Programmes that embed reviews into routine workflows, set stewardship objectives into hospital quality plans and report outcomes to the board tend to last longer [11, 31]. Regular reporting of a few well-chosen indicators, such as DOT per 1000 patient-days for targeted agents, proportion of prescriptions with documented indication and review date, and C. difficile incidence, keeps the topic visible without overwhelming a small team [17, 18]. The WHO toolkit proposes similar stepwise approaches, and the Pulcini checklist offers a way to track progress over time against agreed items [13, 36].

Diagnostic support deserves particular thought in small hospitals. A culture result that arrives on day three is of limited help to a reviewer who must decide at 48 hours, so agreement with the laboratory on reporting times and on telephone notification of positive blood cultures is a basic requirement [11, 31]. Rapid platforms are costly, and the published benefits come mainly from centres that combined them with active team review [25]. Penicillin allergy assessment is a cheaper way to improve prescribing, since a simple structured history can identify low-risk patients who can be challenged under supervision, and delabelling widens the choice of narrow-spectrum drugs [34, 35]. Both activities can be started on a small scale and expanded gradually [12].

6. LIMITATIONS AND FUTURE DIRECTIONS

The literature on stewardship outcomes has weaknesses that apply directly to the conclusions drawn above. Most studies are uncontrolled before-and-after comparisons or interrupted time series, and randomised trials are uncommon, in part because stewardship is delivered at hospital or ward level. Consensus recommendations on research design identified frequent problems, including failure to account for secular trends, poorly defined outcomes, and selective reporting of favourable measures [15]. Publication bias probably favours positive reports. Table 1 should therefore be read as a summary of what has been reported, not a set of estimates of what any particular hospital would achieve [14, 16, 32].

Confounding is a second problem that deserves explicit mention. Patients who are sicker are more likely to receive broad-spectrum drugs and to have worse outcomes, so any association between a prescribing pattern and mortality may reflect case mix and not the drug choice. The pooled analyses of guideline adherence and of programme effects draw on observational studies that adjusted for severity to varying degrees [24, 26]. Likewise, studies of adverse events cannot easily separate harm caused by antibiotics from harm caused by the illness that prompted treatment [41]. Reading the evidence with these limits in mind leads to a cautious but still positive conclusion, namely that stewardship probably does what it claims on use and safety, with less certainty on cost and resistance [28, 30].

Evidence from secondary care and from low-resource settings is thinner than evidence from large academic centres. Many of the pooled analyses draw predominantly on tertiary hospitals in North America and Europe, and extrapolation to hospitals with different staffing, case mix and resistance patterns is uncertain [26, 30]. Reviews from Africa and from low- and middle-income countries describe fewer, smaller and less rigorous studies, even though the burden of resistance is high [8, 39]. There is also little information on the cost of running a programme in a small hospital, which would help managers to judge whether the investment is worthwhile [30, 31].

Future work should focus on better design and wider settings. Cluster-randomised and stepped-wedge trials of well-described intervention bundles in secondary care hospitals would answer questions that observational work cannot, and shared outcome sets, including balancing measures, would allow results to be pooled [15, 16]. Greater use of diagnostic stewardship, rapid

tests and decision support may extend what small teams can do, but needs evaluation in settings with limited infrastructure [19, 25]. Finally, research on how to sustain programmes, and on the effect of stewardship on patient-level harms such as adverse events and allergy mislabelling, would address gaps that matter to clinicians and patients alike [34, 35, 41].

7. CONCLUSION

Published evidence supports antimicrobial stewardship as a safe way to reduce unnecessary antibiotic use in hospital. Reviews and trials agree on shorter treatment, better adherence to policy and lower consumption, and they find no consistent rise in mortality [14, 24, 26]. Effects on C. difficile infection are well supported, and effects on resistant organisms are most convincing when stewardship works alongside infection control [27, 28, 29]. Economic findings favour programmes in direction, though their methods are inconsistent [30]. For a secondary care hospital, these findings suggest that modest, well-chosen interventions can bring real benefit without large specialist teams.

The caveats are equally clear. Most studies are uncontrolled, outcome definitions differ, and secondary care settings are underrepresented in the literature [15, 16, 32]. Practical guidance from the evidence is to start with leadership support and a few high-yield interventions, audit a small number of indicators, protect time for the stewardship lead and report results regularly [12, 18, 31]. Research that uses sound design, shared outcome sets and attention to sustainability would do most to fill the gaps, particularly for small hospitals and for lower-resource settings [15, 36, 39]. Until then, local audit remains the best way to judge whether a programme is working.

8. ABBREVIATIONS

ASP-Antimicrobial stewardship programme, CDC-Centers for Disease Control and Prevention, DDD-Defined daily dose, DOT-Days of therapy, IDSA-Infectious Diseases Society of America, MRSA-Methicillin-resistant Staphylococcus aureus, SHEA-Society for Healthcare Epidemiology of America, WHO-World Health Organization

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10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

12. REFERENCES

1. Magill SS, Edwards JR, Beldavs ZG, Dumyati G, Janelle SJ, Kainer MA, *et al.* Prevalence of antimicrobial use in US acute care hospitals, May–September 2011. JAMA 2014;312:1438–1446.
2. Plachouras D, Kärki T, Hansen S, Hopkins S, Lyytikäinen O, Moro ML, *et al.* Antimicrobial use in European acute care hospitals: results from the second point prevalence survey (PPS) of healthcare-associated infections and antimicrobial use, 2016 to 2017. Euro Surveill 2018;23:1800393.
3. Hecker MT, Aron DC, Patel NP, Lehmann MK, Donskey CJ. Unnecessary use of antimicrobials in hospitalized patients: current patterns of misuse with an emphasis on the antianaerobic spectrum of activity. Arch Intern Med 2003;163:972–978.
4. Fridkin S, Baggs J, Fagan R, Magill S, Pollack LA, Malpiedi P, *et al.* Vital signs: improving antibiotic use among hospitalized patients. MMWR Morb Mortal Wkly Rep 2014;63:194–200.
5. Ferri M, Ranucci E, Romagnoli P, Giaccone V. Antimicrobial resistance: a global emerging threat to public health systems. Crit Rev Food Sci Nutr 2017;57:2857–2876.
6. Spellberg B, Powers JH, Brass EP, Miller LG, Edwards JE Jr. Trends in antimicrobial drug development: implications for the future. Clin Infect Dis 2004;38:1279–86.
7. Gandra S, Barter DM, Laxminarayan R. Economic burden of antibiotic resistance: how much do we really know? Clin Microbiol Infect 2014;20:973–980.
8. Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. Pathog Glob Health 2015;109:309–318.
9. Cosgrove SE, Qi Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y. The impact of methicillin resistance in Staphylococcus

aureus bacteremia on patient outcomes: mortality, length of stay, and hospital charges. Infect Control Hosp Epidemiol 2005;26:166–174.

10. Society for Healthcare Epidemiology of America, Infectious Diseases Society of America, Pediatric Infectious Diseases Society. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infect Control Hosp Epidemiol 2012;33:322–327.
11. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, *et al.* Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis 2016;62:e51–e77.
12. Pollack LA, Srinivasan A. Core elements of hospital antibiotic stewardship programs from the Centers for Disease Control and Prevention. Clin Infect Dis 2014;59(Suppl 3):S97–S100.
13. World Health Organization. Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries: a WHO practical toolkit. Geneva: WHO; 2019.
14. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, *et al.* Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev 2017;2:CD003543.
15. Schweitzer VA, van Werkhoven CH, Rodríguez Baño J, Bielicki J, Harbarth S, Hulscher M, *et al.* Optimizing design of research to evaluate antibiotic stewardship interventions: consensus recommendations of a multinational working group. Clin Microbiol Infect 2020;26:41–50.
16. Hulscher MEJL, Prins JM. Antibiotic stewardship: does it work in hospital practice? A review of the evidence base. Clin Microbiol Infect 2017;23:799–805.
17. Ibrahim OM, Polk RE. Antimicrobial use metrics and benchmarking to improve stewardship outcomes: methodology, opportunities, and challenges. Infect Dis Clin North Am 2014;28:195–214.
18. van den Bosch CMA, Geerlings SE, Natsch S, Prins JM, Hulscher MEJL. Quality indicators to measure appropriate antibiotic use in hospitalized adults. Clin Infect Dis 2015;60:281–291.
19. Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, *et al.* Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. JAMA 2009;302:1059–1066.
20. Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, *et al.* Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database Syst Rev 2017;10:CD007498.
21. Cosgrove SE, Seo SK, Bolon MK, Sepkowitz KA, Climo MW, Diekema DJ, *et al.* Evaluation of postprescription review and feedback as a method of promoting rational antimicrobial use: a multicenter intervention. Infect Control Hosp Epidemiol 2012;33:374–380.
22. Mehta JM, Haynes K, Wileyto EP, Gerber JS, Timko DR, Morgan SC, *et al.* Comparison of prior authorization and prospective audit with feedback for antimicrobial stewardship. Infect Control Hosp Epidemiol 2014;35:1092–1099.
23. Mertz D, Koller M, Haller P, Lampert ML, Plagge H, Hug B, *et al.* Outcomes of early switching from intravenous to oral antibiotics on medical wards. J Antimicrob Chemother 2009;64:188–199.
24. Schuts EC, Hulscher MEJL, Mouton JW, Verduin CM, Stuart JWTC, Overdiek HWPM, *et al.* Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis 2016;16:847–856.
25. Huang AM, Newton D, Kunapuli A, Gandhi TN, Washer LL, Isip J, *et al.* Impact of rapid organism identification via matrix-assisted laser desorption/ionization time-of-flight combined with antimicrobial stewardship team intervention in adult patients with bacteremia and candidemia. Clin Infect Dis 2013;57:1237–1245.
26. Karanika S, Paudel S, Grigoras C, Kalbasi A, Mylonakis E. Systematic review and meta-analysis of clinical and economic outcomes from the implementation of hospital-based antimicrobial stewardship programs. Antimicrob Agents Chemother 2016;60:4840–4852.
27. Feazel LM, Malhotra A, Perencevich EN, Kaboli P, Diekema DJ, Schweizer ML.

Effect of antibiotic stewardship programmes on Clostridium difficile incidence: a systematic review and meta-analysis. J Antimicrob Chemother 2014;69:1748–1754.

28. Baur D, Gladstone BP, Burkert F, Carrara E, Foschi F, Döbele S, *et al.* Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and Clostridium difficile infection: a systematic review and meta-analysis. Lancet Infect Dis 2017;17:990–1001.
29. Lawes T, Lopez-Lozano JM, Nebot CA, Macartney G, Subbarao-Sharma R, Dare CRJ, *et al.* Effects of national antibiotic stewardship and infection control strategies on hospital-associated and community-associated meticillin-resistant Staphylococcus aureus infections across a region of Scotland: a non-linear time-series study. Lancet Infect Dis 2015;15:1438–1449.
30. Nathwani D, Varghese D, Stephens J, Ansari W, Martin S, Charbonneau C. Value of hospital antimicrobial stewardship programs [ASPs]: a systematic review. Antimicrob Resist Infect Control 2019;8:35.
31. Doernberg SB, Abbo LM, Burdette SD, Fishman NO, Goodman EL, Kravitz GR, *et al.* Essential resources and strategies for antibiotic stewardship programs in the acute care setting. Clin Infect Dis 2018;67:1168–1174.
32. Wagner B, Filice GA, Drekonja D, Greer N, MacDonald R, Rutks I, *et al.* Antimicrobial stewardship programs in inpatient hospital settings: a systematic review. Infect Control Hosp Epidemiol 2014;35:1209–1228.
33. Spellberg B. The new antibiotic mantra: shorter is better. JAMA Intern Med 2016;176:1254–1255.
34. Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. Lancet 2019;393:183–198.
35. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy: a review. JAMA 2019;321:188–199.
36. Pulcini C, Binda F, Lamkang AS, Trett A, Charani E, Goff DA, *et al.* Developing core elements and checklist items for global hospital antimicrobial stewardship programmes: a consensus approach. Clin Microbiol Infect 2019;25:20–25.
37. Carling P, Fung T, Killion A, Terrin N, Barza M. Favorable impact of a multidisciplinary antibiotic management program conducted during 7 years. Infect Control Hosp Epidemiol 2003;24:699–706.
38. Holmes AH, Moore LSP, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, *et al.* Understanding the mechanisms and drivers of antimicrobial resistance. Lancet 2016;387:176–187.
39. Akpan MR, Isemin NU, Udoh AE, Ashiru-Oredope D. Implementation of antimicrobial stewardship programmes in African countries: a systematic literature review. J Glob Antimicrob Resist 2020;22:317–324.
40. Cox JA, Vlieghe E, Mendelson M, Wertheim H, Ndegwa L, Villegas MV, *et al.* Antibiotic stewardship in low- and middle-income countries: the same but different? Clin Microbiol Infect 2017;23:812–818.
41. Tamma PD, Avdic E, Li DX, Dzintars K, Cosgrove SE. Association of adverse events with antibiotic use in hospitalized patients. JAMA Intern Med 2017;177:1308–1315.