J Antimicrob Chemother
doi:10.1093/jac/dkx312

Journal of Antimicrobial Chemotherapy

A framework for ensuring a balanced accounting of the impact of antimicrobial stewardship interventions

Madalina Toma[1], Peter G. Davey[2], Charis A. Marwick[2] and Bruce Guthrie[1,2,*]

[1]*Scottish Improvement Science Collaborating Centre (SISCC), School of Nursing and Health Sciences, University of Dundee, 11 Airlie Place, Dundee DD1 4HJ, UK;* [2]*Population Health Sciences Division, School of Medicine, University of Dundee, Kirsty Semple Way, Dundee DD2 4BF, UK*

*Corresponding author. Tel: +44-(0)1382-383740; E-mail: b.guthrie@dundee.ac.uk

Drawing on a Cochrane systematic review, this paper examines the relatively limited range of outcomes measured in published evaluations of antimicrobial stewardship interventions (ASIs) in hospitals. We describe a structured framework for considering the range of consequences that ASIs can have, in terms of their desirability and the extent to which they were expected when planning an ASI: expected, desirable consequences (intervention goals); expected, undesirable consequences (intervention trade-offs); unexpected, undesirable consequences (unpleasant surprises); and unexpected, desirable consequences (pleasant surprises). Of 49 randomized controlled trials identified by the Cochrane review, 28 (57%) pre-specified increased length of stay and/or mortality as potential *trade-offs* of ASI, with measurement intended to provide reassurance about safety. In actuality, some studies found unexpected decreases in length of stay (a *pleasant surprise*). In contrast, only 11 (10%) of 110 interrupted time series studies included any information about unintended consequences, with 10 examining unexpected, undesirable outcomes (*unpleasant surprises*) using case–control, qualitative or cohort designs. Overall, a large proportion of the ASIs reported in the literature only assess impact on their targeted process *goals*—antimicrobial prescribing—with limited examination of other potential outcomes, including microbial and clinical outcomes. Achieving a balanced accounting of the impact of an ASI requires careful consideration of expected undesirable effects (potential *trade-offs*) from the outset, and more consideration of unexpected effects after implementation (both *pleasant* and *unpleasant surprises*, although the latter will often be more important). The proposed framework supports the systematic consideration of all types of consequences of improvement before and after implementation.

Introduction

Increasing antimicrobial resistance poses a major threat to human health. Health services internationally have responded by planning or implementing a range of antimicrobial stewardship interventions (ASIs) to promote judicious use of antimicrobials to preserve their future effectiveness.[1] ASIs are usually complex with multiple components,[2] with expected benefits balanced against unintended adverse consequences such as delayed or ineffective treatment of life-threatening infections.[3–5] Antimicrobial stewardship shares many characteristics with other healthcare quality improvement programmes, including improvers typically focusing on delivering a predefined set of benefits in terms of processes of care. However, any evaluation of the impact of an improvement programme should report all unintended consequences (which may be negative or positive), as well as the targeted processes of care that are intended for improvement.[6] In this paper, we examine the range of outcomes measured in published evaluations of ASIs in hospitals, and describe a framework for thinking about the consequences of interventions to help achieve a balanced accounting of impact.

What outcomes do ASIs measure?

The recently updated Cochrane systematic review of the impact of ASIs in hospital[5] included 221 studies in total, with 49 randomized controlled trials (RCTs) and 110 interrupted time series (ITS) studies contributing to at least one meta-regression or meta-analysis. Reflecting the design of the Cochrane review, all the included RCTs and ITS studies measured antimicrobial outcomes, with 46 RCTs (93.8%) and 101 ITS studies (91.8%) aiming to improve antimicrobial treatment and the remaining 3 RCTs (6.1%) and 9 ITS studies (8.2%) aiming to improve surgical prophylaxis (Table 1).

In contrast, only a minority of studies examined any other type of outcome. Only 5 RCTs (10.2%) and 26 ITS studies (23.6%) examined microbial outcomes, most commonly colonization or infection with resistant bacteria, or *Clostridium difficile* infection (CDI), with an explicit or implicit assumption that these would reduce. Twenty-eight (57.1%) RCTs and 4 (3.6%) ITS studies examined all-cause mortality while length of hospital stay was measured in 15 RCTs (30.6%) and 2 ITS studies (1.8%). However, it was often unclear whether length of stay and mortality were expected to change, and if so, in which direction (whether there was a hope

Table 1. Type of outcome measured in ASIs

Type of outcome measured	RCTs, *n* (%) (*N* = 49)	ITS studies, *n* (%) (*N* = 110[a])
Antimicrobial treatment	46 (93.8)	101 (91.8)
Surgical antimicrobial prophylaxis	3 (6.1)	9 (8.2)
Microbial outcomes	5 (10.2)	26 (23.6)
Mortality	28[b] (57.1)	4[c] (3.6)
Length of hospital stay	15[b] (30.6)	2[c] (1.8)
Other outcomes[d]	23 (46.9)	8 (7.2)

[a]Eleven ITS studies included a control group for comparison.
[b]Thirty-one RCTs in total: 16 mortality only, 12 mortality and length of hospital stay, and 3 length of stay only.
[c]Six ITS studies in total; no study included both mortality and length of hospital stay.
[d]Most commonly measured other outcomes included delays in starting antimicrobial treatment, duration of fever, time spent on mechanical ventilation or increased allergic reactions.

that the ASI would reduce mortality and length of stay, or a fear that they would increase).

Other outcomes relating to the impact and safety of interventions were reported in 23 RCTs (46.9%) and 8 ITS studies (7.2%), usually relating to anticipated (or feared) negative outcomes of stewardship. These included concerns about delays in starting antimicrobial treatment or delays in seeing other patients with urgent needs in the emergency department, and concerns about changes in antimicrobial use causing acute kidney injury (AKI), longer duration of fever, increased duration of mechanical ventilation, increased allergic reactions or increased surgical site infections.

Overall, the review authors concluded that they had found high-certainty evidence that ASIs are effective in increasing compliance with antimicrobial policy and reducing duration of antimicrobial treatment, and that lower use of antimicrobials likely reduces length of stay and probably does not increase mortality. Additional trials comparing antimicrobial stewardship with no intervention are unlikely to change these conclusions. Reflecting the limited range of outcomes examined by the included studies, more research was recommended to examine the wide range of unintended consequences of restrictive interventions.

What kinds of consequences should implementers of ASIs consider?

There is no clear consensus on what outcomes should be measured to evaluate the impact of ASIs. Professional organizations have proposed that alongside the process measures of antimicrobial use that dominate the existing literature, interventions should measure patient outcomes (mortality, length of hospital stay and readmission rates) and unintended consequences.[7–9] In practice, antimicrobial stewardship trialists and improvers have to make choices about what to measure given available resources. This paper describes an approach based on quality improvement work in other contexts to help plan measurement strategies in a structured way to ensure a balanced accounting of antimicrobial stewardship impact.

As with other improvement interventions, there are two prominent features of the types of measure used to evaluate effectiveness in the studies examined. These are whether outcomes are desirable or undesirable, and whether outcomes are expected or not. Of note is that for some outcomes desirability depends on the expected direction of change (an obvious example being that *reduced* mortality is desirable, whereas *increased* mortality is undesirable), but many published papers do not clearly state their expectations before implementation. Potential metrics can therefore be divided into four main categories, any of which can be measured in terms of process and outcome, both in the clinical setting targeted by improvement and other clinical settings in which consequences might occur (for example due to readmission to other services). The four types of consequence are adapted from the diffusion of innovations literature[10–14] and described in Figure 1:

- ASI goals: the expected and desirable consequences of the improvement intervention.
- ASI trade-offs: the expected but undesirable consequences of the improvement intervention. Before intervention, these are assumed to be smaller in magnitude than the goals (and so implicitly are an acceptable compromise), but may include outcomes such as mortality where any significant increase is likely to outweigh improvement in goals and which are often measured to reassure about safety.
- ASI pleasant surprises: unexpected and desirable consequences emerging after implementation.
- ASI unpleasant surprises: unexpected and undesirable consequences emerging after implementation.

Examples of goals, trade-offs and surprises in the antimicrobial stewardship literature

ASI goals (expected desirable consequences)

Overall, the primary goal of ASIs is to reduce total or specific antimicrobial use. All the interventions included in the review measured antimicrobial prescribing but only a minority clearly specified other types of goal, such as microbial outcomes. Other pre-specified goals included reduced length of stay and/or reduced in-hospital mortality in 31 (63%) RCTs but only 6 (5%) ITS studies evaluating stewardship interventions intended to change antimicrobial prescribing (Table 1).

ASI trade-offs (expected undesirable consequences)

Several studies pre-specified increased mortality and increased length of stay as expected undesirable consequences, with measurement intended to allow examination of trade-offs (length of stay) or provide reassurance about safety (mortality). For instance, two RCTs[15,16] explicitly framed length of stay and mortality as 'safety outcomes' because they were concerned that both might increase, although neither actually did. Similarly, even in a context where the improvers expected their intervention to reduce length of stay, they were concerned that this might lead to higher rates of rapid readmission and measured the latter as a predefined trade-off.[17] In studies in emergency departments, some authors were concerned that prioritizing rapid antimicrobial administration for patients with fever and neutropenia might compromise care for other patients. The initial measurement plans therefore included

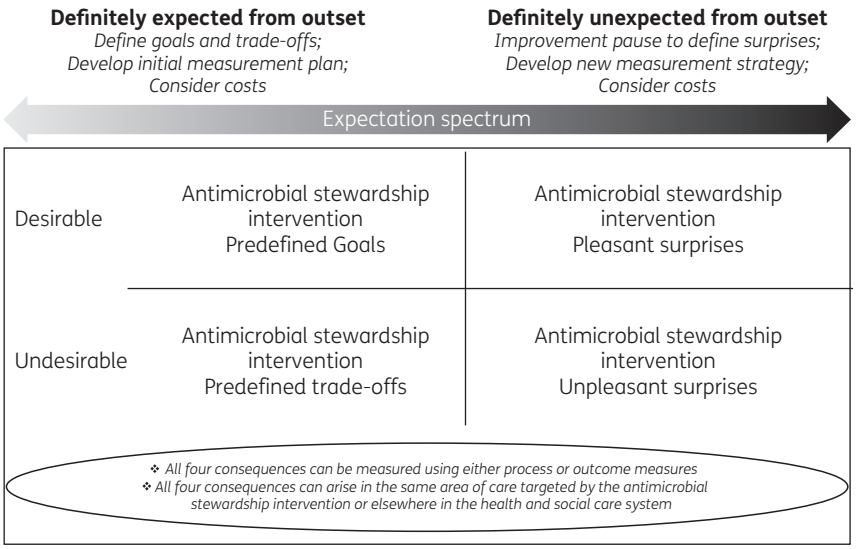

Figure 1. Types of consequences of ASI.

trade-offs between achieving the goals of more rapid initiation of antimicrobials and potential treatment delays for patients with other urgent problems[18,19] and/or an expected increase in patients leaving without being seen.[20] In the latter study, other potential trade-offs identified before implementation included the intervention effect on nurses' workload when a febrile neutropenic patient was placed in their nursing area and the potential for staff to develop user fatigue, but the improvers chose not to explicitly measure these.[20]

Pleasant surprises (unexpected desirable consequences)

Some consequences are not expected before implementation, and therefore only become visible or apparent subsequently. For instance, three RCTs pre-specified length of stay as a trade-off (that is, they expected or feared an *increase* due to the stewardship intervention), but actually found unexpected *decreases* (a pleasant surprise).[21–23] A few studies explicitly examined other outcomes that were unexpected and desirable, such as an observed reduction in delay to first antimicrobial treatment from an intervention that aimed to reduce the number of unnecessary diagnostic tests in infants with risk factors for early-onset neonatal sepsis.[24] More commonly, papers speculated that there were unmeasured pleasant surprises; for example, discussion of an intervention to discontinue unnecessary intravenous antimicrobial therapy suggested that there were '*unmeasured theoretical benefits*' in terms of reduced incidence of phlebitis or other potential complications.[25]

Unpleasant surprises (unexpected undesirable consequences)

Only 10 studies in the Cochrane review examined unexpected or surprising negative outcomes. When outcomes are unexpected, then data have not typically been collected before and after intervention implementation, and studies most commonly examined unpleasant surprises using case–control, qualitative and cohort designs. For example, a case–control study investigating an abrupt and persistent 30% increase in the absolute number of reported nosocomial infections found it was actually a pseudo-outbreak caused by physicians altering their threshold for diagnosis and reporting in response to implementation of a restrictive antimicrobial policy.[26] In response to a similarly restrictive intervention, qualitative interviews with clinical staff revealed unexpected difficulties with the prior approval process for restricted antimicrobials, including failure to clearly document approval and ambiguity in the duration of approval. The consequences were erosion of trust in the accuracy of feedback data about appropriate use of restricted antimicrobials.[27]

Four cohort studies investigated post-implementation concerns about restrictive interventions that had arisen some years after the implementation of ASIs (Table 2). The aims of these studies varied considerably in that one was intended to provide reassurance about the risks of automatic stop orders[28] whereas the other three were intended to confirm concerns about prior approval programmes.[29–31] As reported, the results did not reveal any surprises *per se* because the authors interpreted them as supporting their predictions that stop orders would be safe and that requiring prior approval carried risks (Table 2). These conclusions would have been much stronger if the studies had explicitly addressed the potential trade-offs involved. For example, how much delay in vancomycin treatment in how many patients would it take to consider modifying a stop order policy?

Three cohort studies addressed concerns that public reporting of hospital performance on a national quality indicator of timely treatment of patients with community-acquired pneumonia (CAP) might be leading to unnecessary antibiotic treatment of patients who did not have pneumonia.[32–34] These concerns were supported by additional studies that were not included in the Cochrane review,[35] and the performance measure was subsequently revised and then withdrawn altogether.[36]

One study used an ITS design to address post-implementation concerns that a change in surgical prophylaxis policy from

Table 2. Cohort studies of unintended consequences of restrictive interventions

Study	Restrictive intervention	Source of concern	Measures and results	Author conclusions
Connor *et al.*[28] 2007	Automatic stop order for vancomycin after 72 h of treatment.[58]	Stop orders may lead to inadvertent discontinuation or interruption of appropriate therapy.	Interruption of vancomycin: 1. Frequency 8% 2. Duration 6–36 h	'Automatic stop orders are unlikely to pose a substantial risk of denying necessary antibiotic therapy to patients. These data should provide reassurance to ASPs that are considering instituting automatic stop orders.'
LaRosa *et al.*[29] 2007	A prior approval ASP that was active between 8 am and 11 pm.[58]	In a prior qualitative study at the same hospital some house staff stated that they engaged in 'stealth dosing' (waiting until after the prior-approval period ended to prescribe restricted antimicrobial drugs).[49]	1. Prescribing of restricted antibiotics was 57% of total 11–12 pm versus 50% 10–11 pm 2. Restricted therapy continued for >1 day 65% after 11 pm versus 89% before 11 pm	'Although ASPs have been shown to be beneficial, our findings reflect a potential limitation of these programes. Further efforts to identify and correct the limitations of existing ASPs are needed to optimise their usefulness.'
Linkin *et al.*[30] 2007	A prior approval ASP that was active between 8 am and 11 pm.[58]	Data communicated from clinicians were found to contain inaccurate patient information in >40% of calls made to practitioners in a prior study of this hospital's ASP.[48]	Inappropriate antimicrobial therapy[a] with inaccurate data versus other calls: 1. Any data inaccurate: OR 2.2, CI 1.1–4.6 2. Microbiological data inaccurate: OR 7.5, CI 2.1–27.0	'Studies are needed to test and extend our findings by evaluating other causes of inappropriate recommendations, downstream clinical outcomes, and the effect of technological interventions.''Clinicians and ASP practitioners should confirm critical communicated data before use in prescribing decisions.'
Winters *et al.*[31] 2010	A prior approval ASP. Stat doses of restricted antimicrobials could be ordered without approval 10 pm to 8 am but not during the day. Year of introduction of ASP not clear	Prior approval may delay time to first antibiotic dose	Delays when the antimicrobial was restricted versus not restricted: 1. 1 h a. 8 am–10 pm: 46% versus 36% b. 10 pm–8 am: 39% versus 36% 2. ≥2 h a. 8 am–10 pm: 24% versus 16% b. 10 pm–8 am: 15% versus 14%	'Delays in antimicrobial administration should be kept to a minimum and avoided altogether in critically ill patients. One way to accomplish this might be to not require approval for the first administration of a stat antibiotic but require approval of subsequent doses.'

ASPs, antimicrobial stewardship programmes.
[a]Most common reason for rating a recommendation as inappropriate was that antimicrobial therapy was not indicated.

cefuroxime to flucloxacillin plus gentamicin may have increased risk of post-operative AKI in orthopaedic patients.[37] The results confirmed a clinical impression of increased AKI, and resulted in a further change to the prophylaxis policy (described in detail in Table 3 and below).

Challenges associated with achieving a balanced accounting of ASI impact

The framework described in Figure 1 has the benefit of bringing a systematic approach to considering the consequences of ASIs, which is important because decisions often have to be made in the face of considerable uncertainty and then adapted to new information. This is illustrated by the experience of the development, implementation and modification of an ASI intended to reduce the use of surgical antimicrobial prophylaxis associated with higher risk of CDI in one Scottish Health Board (Table 3).[37] AKI risk was explicitly considered pre-intervention, in response to clinician concern about AKI risks in changing surgical prophylaxis to gentamicin plus flucloxacillin, and the planned intervention was amended in the patient group at highest risk of AKI (patients with fractured neck of femur). However, it was also decided that routine

Table 3. Potential challenges in achieving a balanced accounting of intervention impact: changing policies for surgical prophylaxis in one Scottish Health Board

In response to high rates of CDI, the Antibiotic Management Group in the 855 bed Ninewells Hospital in NHS Tayside introduced a number of measures intended to reduce the use of antibiotics associated with a high risk of CDI in analysis of local data.[59] Antimicrobial prophylaxis for orthopaedic implant surgery was changed from single-dose cefuroxime 1.5 g to four doses of flucloxacillin 1 g plus single-dose gentamicin 4 mg/kg. During intervention planning, concerns were raised about the renal risks of the new regimen in patients with fractured neck of femur who are older and have higher prevalence of chronic kidney disease, resulting in the recommendation to use co-amoxiclav (which although still relatively high risk for CDI remained on the formulary for some indications, whereas cefuroxime did not). There was no plan to measure rates of AKI in either group of orthopaedic patients because AKI risks from the chosen single-dose prophylaxis in each group were considered remote (i.e. a *trade-off* was not considered likely).
In 2012, another Scottish hospital reported concerns about increased rates of post-operative AKI in orthopaedic patients from the same change in surgical prophylaxis.[60] In response to this concern, NHS Tayside carried out an ITS analysis with the belief that it would refute the concern. The analysis unexpectedly confirmed increased rates of AKI in orthopaedic surgery but not in other types of surgery (a very *unpleasant surprise*),[37] with a subsequent reduction in AKI when antimicrobial prophylaxis was changed to co-amoxiclav for all types of orthopaedic surgery.[61]
More detailed analysis has shown that AKI rates did not change after the first change in policy in 2008 for people with fractured neck of femur (who had a switch from cefuroxime to co-amoxiclav; pre-intervention 15.0% versus post-intervention 14.8%) although CDI rates in this group more than halved (3.6% versus 1.7%). For other implant surgery where prophylaxis changed from cefuroxime to flucloxacillin/gentamicin, AKI rates pre- and post-intervention were 6.2% and 10.8%, and *C. difficile* rates were 0.8% versus 0.4%, confirming that any possible benefit in terms of reduced CDI in this group was likely to be much smaller than the increased potential harm in terms of AKI.

measurement of AKI was not required as the cost outweighed what was considered a remote risk in other patients. Post-implementation, further clinical concerns that there had been increases in AKI in the lower-risk group of patients receiving gentamicin and flucloxacillin prompted rigorous investigation to quantify whether the perceived risk was real. However, the Antimicrobial Management Group (AMG) was expecting the analysis to refute the clinical concerns, and had not considered what to do if the analysis confirmed that there was a problem. When the analysis showed that gentamicin plus flucloxacillin was causing at least 10 additional cases of AKI per month in NHS Tayside, there was then a need for rapid decisions to be made with the Health Board Director of Pharmacy, Medical Director and Chief Executive about how to respond. Decision-making was complicated by the difficulties of weighing up any potential gain in lower rates of CDI against the potential harm of higher rates of AKI, but as the number of people developing AKI was ~10 times the number who might have avoided CDI as a result of the intervention, the surgical prophylaxis policy was changed to minimize AKI risk.

Implications for antimicrobial stewardship programmes

Implications for doing and evaluating improvement

Although the focus of this paper is on choice of outcomes, Antimicrobial Management Teams (AMTs) will also have to ensure that their evaluation design delivers results that are internally valid in terms of being as resistant to confounding and bias as possible. Although RCTs remain the gold standard for ensuring internal validity, the Cochrane Effective Practice and Organisation of Care Group also considers that other study designs can allow reasonable inference of causality including trials that allocate non-randomly, controlled before-and-after studies, and ITS studies.[38] In the field of antimicrobial stewardship, though, the choice for those with research funding is more likely to be between cluster RCTs (cRCTs) and ITS designs,[39] (ideally controlled ITS where there is a comparison with a setting without an intervention), with ITS designs the most feasible evaluation design for clinicians and managers seeking to evaluate a local stewardship intervention.[40]

Assessing the full value of ASIs requires a balanced accounting of the costs, risks and benefits, but assessment will often be resource constrained, meaning that AMTs have to make choices about what to measure in the face of uncertainty due to the difficulty predicting how a complex, dynamic system will respond to change.[10,41] Before beginning or expanding a stewardship programme, the AMTs therefore need to plan their measurement strategy, brainstorming goals and trade-offs, articulate assumptions around the expected direction of change, and speculate on potential surprises and how they might be revealed. The aim should be to identify ASI goals and likely trade-offs, and then to determine which should be measured. Indeed, many undesirable outcomes are predictable and should be accounted for from the outset. It should no longer be any surprise to an AMT that stop orders or requirements for prior approval have the potential to interrupt or delay treatment (Table 2), or that performance measurement of time to first antibiotic for patients with CAP may lead to unnecessary antibiotic treatment in patients who do not have pneumonia.[35] Consequently, AMTs considering an ASI using these methods should always consider whether measurement of predictable trade-offs is needed,[42] although AMTs still need to carefully identify other likely consequences of their particular ASI in their specific context.

Plan-Do-Study-Act (PDSA) cycles are a practical method for identifying consequences.[43–45] However, the application of the PDSA methodology to healthcare has often resulted in an over-

Table 4. Strategies for minimizing the unintended consequences of performance measurement[50] and examples of studies from the Cochrane review[5]

Strategy	Examples from the Cochrane review
Involve staff at all levels	Forming inter-professional improvement teams with front-line staff involving senior and junior doctors, nurses and pharmacists.[20,62] Involving management at clinical service and hospital levels.[20,62] Involving junior doctors[63] and other front-line staff[19,20] such as pharmacists in interpreting and learning from collected data.
Retain flexibility in the use of performance indicators	Using process maps to identify performance indicators and tests of change to modify them.[20,62] Using run charts to identify outliers and chart review to investigate causes and targets for change.[20] Using staff coaching to identify factors contributing to performance lapses and invite suggestions for improvement.[19]
Quantify every important outcome	Two studies identified delay in treatment of other patients as a potential consequence of reducing time to first antibiotic dose for children with sepsis in emergency departments.[19,20] However, only one went on to test and implement quantitative measures of identified trade-offs (time left without being seen for all patients in the emergency department and time to first dose of β-agonist for children with asthma).[20]
Keep system under constant review	Specifying two or more intervention periods to allow review of consequences and adaptation of intervention.[19,20,62]

simplified 'Do, Do, Do' approach focused on desired *goals* at the expense of study and reflection before and after implementation, which means that improvement teams often fail to account for unexpected consequences and may not maximize benefit.[46] Two systematic reviews of application of PDSA methods to healthcare state that they can reveal unanticipated consequences of change, but neither actually includes a detailed consideration of the full range of consequences in their data synthesis framework.[45,47] Only one of these reviews included any information about reporting of consequences, finding that only 6 (6.4%) of 94 included studies reported 'disconfirming observations' about the intervention.[47]

Furthermore, the Cochrane review identified that only a small minority of studies explicitly addressed unintended consequences, and it is notable that four (including the only RCT) were from the same institution (the University of Pennsylvania School of Medicine).[18,28,29,48] These studies were informed by previous research from the same hospital, which investigated the unintended effects of computerized physician orders with focus groups, interviews, shadowing and observation of house staff, nurses, information technology leaders, pharmacy leaders and attending physicians.[49] It is likely that this research increased awareness about unintended consequences of the ASI at this hospital. However, considering unexpected consequences should be the rule rather than the exception. An 'improvement pause' to take stock at a planned time after implementation will allow teams to consider whether there is enough evidence that surprises have happened to make it worth systematically measuring their impact.

In this regard, antimicrobial stewardship programmes need to learn from experience of performance measurement[50] and systems analysis[41] in other sectors. Most of the consequences identified by the review arise from one of the commonest problems with performance measurement: tunnel vision, where what is measured leads to neglect of unmeasured aspects of performance. However, the Cochrane review also found examples of misrepresentation of microbiological results,[26,30] misinterpretation of information about appropriateness of prescription of restricted antibiotics,[27] and workarounds to avoid prior approval policies.[29] Four strategies have been recommended to minimize the risk of tunnel vision, misrepresentation and misinterpretation: involving staff at all levels; retaining flexibility in the use of performance indicators; quantifying every important outcome; and keeping the system under constant review.[50] There are examples of studies in the Cochrane review[5] that employed these strategies (Table 4), and they are aligned to the framework in terms of working with stakeholders to identify and measure a balanced set of processes and outcomes, and ensuring post-implementation review to identify and measure significant unpleasant surprises.

Although measurement is central to improvement, qualitative methods have much to offer in the identification of unexpected consequences to maximize benefit.[10,43,44] Qualitative methods can be used to help design interventions, exemplified by the Reducing Antibiotic Prescribing in Dentistry (RAPiD) study, which used data about community dentists' perceptions of consequences of using surgical treatment rather than antimicrobials to design a behavioural change intervention.[51] Qualitative methods can also support post-implementation study and reflection. It is to be expected that clinicians will sometimes evade restrictive antimicrobial stewardship policies[27] in ways that undermine the intervention, but the existence, rationale and form of workarounds can also be evidence that clinicians perceive the restriction to be difficult to safely fit into clinical workflows and that the intervention therefore needs adaptation.[41,43]

Implications for reporting improvement interventions

The Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0) recommend that reporting of results should include 'unintended consequences, such as unexpected benefits, problems, failures or costs associated with the intervention' (standard 13e).[6]

However, the detailed explanation and elaboration document does not specifically mention this or provide an example,[52] and the measurement element (standard 10) focuses on process and outcome measures without specifying that these can evaluate both positive and negative consequences.[6] Similarly, although the Outbreak Reports and Intervention studies Of Nosocomial Infection (ORION) guidelines require the reporting of any harms measured,[53] neither the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE)[54] nor the proposed antimicrobial stewardship extension (STROBE-AMS) reporting standards[55] specifically mention unintended consequences in discussion of outcomes. Irrespective of which reporting standard is most appropriate to any individual study, we recommend that reports of ASIs (and other improvement interventions) should describe how the initial improvement plan was developed, including whether and how expected undesirable consequences (trade-offs) were accounted for, whether there were post-implementation surprises, and whether they were measured. Analysis should report all measured positive and negative consequences and a balanced interpretation across all measures.

Conclusions

A large proportion of the ASIs reported in the literature only assess impact on their targeted process *goals*—antimicrobial prescribing—with limited examination of other potential goals, including microbial and clinical outcomes. Reflecting this and the high certainty that stewardship improves prescribing in *hospitals*, the Cochrane review concluded that 'future research should instead focus on measuring clinical outcomes and assessing other measures of patient safety and different stewardship interventions and explore the barriers and facilitators to implementation' (p. 31).[5] There is, however, less certainty about the effects of ASIs in the *community*, although it will be equally important to study a balanced set of outcomes in that context.

Achieving a balanced accounting of the impact of an ASI in both hospital and community settings requires careful consideration of expected undesirable effects (potential *trade-offs*) from the outset, and more consideration of unexpected effects after implementation (both *pleasant* and *unpleasant surprises*, although the latter will often be more important). Consensus studies to establish a core outcome set for studies of ASIs would be useful,[56,57] but the proposed framework supports the systematic consideration of all consequences of improvement before and after implementation.

Acknowledgements

We are grateful to The Health Foundation and the British Society for Antimicrobial Chemotherapy for co-funding a workshop on 'The Challenge of Antimicrobial Stewardship in Hospitals: Seeking Solutions from Improvement Science' held at The Health Foundation in London on 12 February 2016.

Funding

This work was supported by The Scottish Improvement Science Collaborating Centre (SISCC), funded by the Scottish Funding Council, Chief Scientist Office, NHS Education for Scotland and The Health Foundation with in-kind contributions from participating partner universities and health boards. The review that formed the basis for this paper was supported by the Chief Scientist Office (Grant CZH4861) and the British Society for Antimicrobial Chemotherapy. The funding bodies had no role in the design of the study, in analysis and interpretation of data and in writing the manuscript.

Transparency declarations

None to declare.

Author contributions

P. G. D. and C. A. M. carried out the Cochrane review on which this paper draws. M. T. and B. G. were responsible for planning and leading the data extraction and analysis for this paper, and all authors contributed to analysis and interpretation. M. T. led the writing of the manuscript and redrafted in response to team input. B. G., P. G. D. and C. A. M. participated in critically appraising and revising the intellectual content of the manuscript. All authors read and approved the final manuscript.

Disclaimer

The views and opinions expressed are those of the authors.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

References

1 NICE. *Antimicrobial Stewardship: Systems and Processes for Effective Antimicrobial Medicine Use*. 2005. https://www.nice.org.uk/guidance/ng15/resources/antimicrobial-stewardship-systems-and-processes-for-effective-antimicrobial-medicine-use-1837273110469.

2 Craig P, Dieppe P, Macintyre S *et al*. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ* 2008; **337**: 979–83.

3 Davey P, Brown E, Charani E *et al*. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2013; issue **4**: 1–208.

4 Davey P, Brown E, Fenelon L *et al*. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2005; issue **4**: 1–116.

5 Davey P, Marwick CA, Scott CL *et al*. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2017; issue **2**: 1–368.

6 Ogrinc G, Davies L, Goodman D *et al*. SQUIRE 2.0 (Standards for Quality Improvement Reporting Excellence): revised publication guidelines from a detailed consensus process. *BMJ Qual Saf* 2016; **25**: 986–92.

7 Morris AM. Antimicrobial stewardship programs: appropriate measures and metrics to study their impact. *Curr Treat Options Infect Dis* 2014; **6**: 101–12.

8 Dellit TH, Owens RC, McGowan JE *et al*. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 2007; **44**: 159–77.

9 Akpan M, Ahmad R, Shebl N *et al*. A review of quality measures for assessing the impact of antimicrobial stewardship programs in hospitals. *Antibiotics* 2016; **5**: 1–26.

10 Rogers EM. *Diffusion of Innovations*. New York: Free Press, 1995.

11 Ash JS, Sittig DF, Dykstra RH *et al*. Categorizing the unintended sociotechnical consequences of computerized provider order entry. *Int J Med Inform* 2007; **76**: 21–7.

12 Ash JS, Sittig DF, Poon EG *et al*. The extent and importance of unintended consequences related to computerized provider order entry. *J Am Med Inform Assoc* 2007; **14**: 415–23.

13 Bloomrosen M, Starren J, Lorenzi NM *et al*. Anticipating and addressing the unintended consequences of health IT and policy: a report from the AMIA 2009 Health Policy Meeting. *J Am Med Inform Assoc* 2011; **18**: 82–90.

14 Campbell EM, Sittig DF, Ash JS *et al*. Types of unintended consequences related to computerized provider order entry. *J Am Med Inform Assoc* 2006; **13**: 547–56.

15 Christ-Crain M, Jaccard-Stolz D, Bingisser R *et al*. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet* 2004; **363**: 600–7.

16 Kristoffersen KB, Sogaard OS, Wejse C *et al*. Antibiotic treatment interruption of suspected lower respiratory tract infections based on a single procalcitonin measurement at hospital admission—a randomized trial. *Clin Microbiol Infect* 2009; **15**: 481–7.

17 Mittal V, Darnell C, Walsh B *et al*. Inpatient bronchiolitis guideline implementation and resource utilization. *Pediatrics* 2014; **133**: e730–7.

18 Strom BL, Schinnar R, Aberra F *et al*. Unintended effects of a computerized physician order entry nearly hard-stop alert to prevent a drug interaction: a randomized controlled trial. *Arch Intern Med* 2010; **170**: 1578–83.

19 Jobson M, Sandrof M, Valeriote T *et al*. Decreasing time to antibiotics in febrile patients with central lines in the emergency department. *Pediatrics* 2015; **135**: e187–95.

20 Volpe D, Harrison S, Damian F *et al*. Improving timeliness of antibiotic delivery for patients with fever and suspected neutropenia in a pediatric emergency department. *Pediatrics* 2012; **130**: e201–10.

21 Fraser GL, Stogsdill P, Dickens JD *et al*. Antibiotic opitimization: an evaluation of patient safety and economic outcomes. *Arch Intern Med* 1997; **157**: 1689–94.

22 Burton ME, Ash CL, Hill DP *et al*. A controlled trial of the cost benefit of computerized bayesian aminoglycoside administration. *Clin Pharmacol Ther* 1991; **49**: 685–94.

23 Paul M, Andreassen S, Tacconelli E *et al*. Improving empirical antibiotic treatment using TREAT, a computerized decision support system: cluster randomized trial. *J Antimicrob Chemother* 2006; **58**: 1238–45.

24 Duvoisin G, Fischer C, Maucort-Boulch D *et al*. Reduction in the use of diagnostic tests in infants with risk factors for early-onset neonatal sepsis does not delay antibiotic treatment. *Swiss Med Wkly* 2014; **144**: w13981.

25 Bailey TC, Ritchie DJ, McMullin ST *et al*. A randomized, prospective evaluation of an interventional program to discontinue intravenous antibiotics at two tertiary care teaching institutions. *Pharmacotherapy* 1997; **17**: 277–81.

26 Calfee DP, Brooks J, Zirk NM *et al*. A pseudo-outbreak of nosocomial infections associated with the introduction of an antibiotic management programme. *J Hosp Infect* 2003; **55**: 26–32.

27 Baysari MT, Oliver K, Egan B *et al*. Audit and feedback of antibiotic use: utilising electronic prescription data. *Appl Clin Inform* 2013; **4**: 583–95.

28 Connor DM, Binkley S, Fishman NO *et al*. Impact of automatic orders to discontinue vancomycin therapy on vancomycin use in an antimicrobial stewardship program. *Infect Control Hosp Epidemiol* 2007; **28**: 1408–10.

29 LaRosa LA, Fishman NO, Lautenbach E *et al*. Evaluation of antimicrobial therapy orders circumventing an antimicrobial stewardship program: investigating the strategy of "stealth dosing". *Infect Control Hosp Epidemiol* 2007; **28**: 551–6.

30 Linkin DR, Fishman NO, Landis JR *et al*. Effect of communication errors during calls to an antimicrobial stewardship program. *Infect Control Hosp Epidemiol* 2007; **28**: 1374–81.

31 Winters BD, Thiemann DR, Brotman DJ. Impact of a restrictive antimicrobial policy on the process and timing of antimicrobial administration. *J Hosp Med* 2010; **5**: E41–5.

32 Friedberg MW, Mehrotra A, Linder JA. Reporting hospitals' antibiotic timing in pneumonia: adverse consequences for patients? *Am J Manag Care* 2009; **15**: 137–44.

33 Kanwar M, Brar N, Khatib R *et al*. Misdiagnosis of community-acquired pneumonia and inappropriate utilization of antibiotics: side effects of the 4-h antibiotic administration rule. *Chest* 2007; **131**: 1865–9.

34 Welker JA, Huston M, McCue JD. Antibiotic timing and errors in diagnosing pneumonia. *Arch Intern Med* 2008; **168**: 351–6.

35 Wachter RM, Flanders SA, Fee C *et al*. Public reporting of antibiotic timing in patients with pneumonia: lessons from a flawed performance measure. *Ann Intern Med* 2008; **149**: 29–32.

36 Chassin MR, Loeb JM, Schmaltz SP *et al*. Accountability measures—using measurement to promote quality improvement. *N Engl J Med* 2010; **363**: 683–8.

37 Bell S, Davey P, Nathwani D *et al*. Risk of AKI with gentamicin as surgical prophylaxis. *J Am Soc Nephrol* 2014; **25**: 2625–32.

38 Cochrane Effective Practice and Organisation of Care (EPOC). *What Study Designs Should be Included in an EPOC Review? EPOC Resources for Review Authors*. 2017. http://epoc.cochrane.org/resources/epoc-resources-review-authors.

39 De Kraker MEA, Abbas M, Huttner B *et al*. Good epidemiological practice: a narrative review of appropriate scientific methods to evaluate the impact of antimicrobial stewardship interventions. *Clin Microbiol Infect 2017*. doi:10.1016/j.cmi.2017.05.019.

40 Wagner AK, Soumerai SB, Zhang F *et al*. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther* 2002; **27**: 299–309.

41 Holden RJ, Carayon P, Gurses AP *et al*. SEIPS 2.0: a human factors framework for studying and improving the work of healthcare professionals and patients. *Ergonomics* 2013; **56**: 1669–86.

42 National Clinical Effectiveness Committee. *Sepsis Management: National Clinical Guideline No. 6*. 2014. http://health.gov.ie/wp-content/uploads/2015/01/National-Clinical-Guideline-No.-6-Sepsis-Management-Nov2014.pdf.

43 Damschroder LJ, Aron DC, Keith RE *et al*. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implement Sci* 2009; **4**: 50.

44 Powell AE, Rushmer RK, Davies HTO. A systematic narrative review of quality improvement models in health care. Healthcare Improvement Scotland 2009; http://www.healthcareimprovementscotland.org/previous_resources/hta_report/a_systematic_narrative_review.aspx.

45 Taylor MJ, McNicholas C, Nicolay C *et al*. Systematic review of the application of the plan-do-study-act method to improve quality in healthcare. *BMJ Qual Saf* 2014; **23**: 290–8.

46 Reed JE, Card AJ. The problem with Plan-Do-Study-Act cycles. *BMJ Qual Saf* 2016; **25**: 147–52.

47 Curnock E, Ferguson J, McKay J *et al*. Healthcare improvement and rapid PDSA cycles of change: a realist synthesis of the literature. *NHS Education for Scotland* 2012. http://www.nes.scot.nhs.uk/media/1389875/pdsa_realist_synthesis.pdf.

48 Linkin DR, Paris S, Fishman NO *et al*. Inaccurate communications in telephone calls to an antimicrobial stewardship program. *Infect Control Hosp Epidemiol* 2006; **27**: 688–94.

49 Koppel R, Metlay JP, Cohen A *et al*. Role of computerized physician order entry systems in facilitating medication errors. *JAMA* 2005; **293**: 1197–203.

50 Smith P. On the unintended consequences of publishing performance data in the public sector. *Int J Publ Admin* 1995; **18**: 277–310.

51 Newlands R, Duncan EM, Prior M *et al*. Barriers and facilitators of evidence-based management of patients with bacterial infections among general dental practitioners: a theory-informed interview study. *Implement Sci* 2016; **11**: 11.

52 Goodman D, Ogrinc G, Davies L *et al*. Explanation and elaboration of the SQUIRE (Standards for Quality Improvement Reporting Excellence) Guidelines, V.2.0: examples of SQUIRE elements in the healthcare improvement literature. *BMJ Qual Saf* 2016; **25**: e7.

53 Stone SP, Cooper BS, Kibbler CC *et al*. The ORION statement: guidelines for transparent reporting of outbreak reports and intervention studies of nosocomial infection. *Lancet Infect Dis* 2007; **7**: 282–8.

54 Vandenbroucke JP, von Elm E, Altman DG *et al*. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology* 2007; **18**: 1628–54.

55 Tacconelli E, Cataldo MA, Paul M *et al*. STROBE-AMS: recommendations to optimise reporting of epidemiological studies on antimicrobial resistance and informing improvement in antimicrobial stewardship. *BMJ Open* 2016; **6**: e010134.

56 The COMET Initiative. http://www.comet-initiative.org.

57 Williamson PR, Altman DG, Blazeby JM *et al*. Developing core outcome sets for clinical trials: issues to consider. *Trials* 2012; **13**: 132.

58 Gross R, Morgan AS, Kinky DE *et al*. Impact of a hospital-based antimicrobial management program on clinical and economic outcomes. *Clin Infect Dis* 2001; **33**: 289–95.

59 Vernaz N, Hill K, Leggeat S *et al*. Temporal effects of antibiotic use and *Clostridium difficile* infections. *J Antimicrob Chemother* 2009; **63**: 1272–5.

60 Challagundla SR, Knox D, Hawkins A *et al*. Renal impairment after high-dose flucloxacillin and single-dose gentamicin prophylaxis in patients undergoing elective hip and knee replacement. *Nephrol Dial Transplant* 2013; **28**: 612–9.

61 Walker H, Patton A, Bayne G *et al*. Reduction in post-operative acute kidney injury following a change in antibiotic prophylaxis policy for orthopaedic surgery: an observational study. *J Antimicrob Chemother* 2016; **71**: 2598–605.

62 Weinberg M, Fuentes JM, Ruiz AI *et al*. Reducing infections among women undergoing cesarean section in Colombia by means of continuous quality improvement methods. *Arch Intern Med* 2001; **161**: 2357–65.

63 Lee TC, Frenette C, Jayaraman D *et al*. Antibiotic self-stewardship: trainee-led structured antibiotic time-outs to improve antimicrobial use. *Ann Intern Med* 2014; **161**: S53–8.