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

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

3

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18

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29 **Synopsis**

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

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## 57 **Introduction**

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

70

## 71 **What outcomes do ASI measure?**

72 The recently updated Cochrane systematic review of the impact of ASI in hospital<sup>5</sup> included 221 studies  
73 in total, with 49 randomised controlled trials (RCTs) and 110 interrupted time series (ITS) studies  
74 contributing to at least one meta-regression or meta-analysis. Reflecting the design of the Cochrane  
75 review, all the included RCTs and ITS studies measured antimicrobial outcomes, with 46 RCTs (93.8%)  
76 and 101 ITSs (91.8%) aiming to improve antimicrobial treatment and the remaining three RCTs (6.1%)  
77 and nine ITS studies (8.2%) aiming to improve surgical prophylaxis (Table 1).

78

79 In contrast, only a minority of studies examined any other type of outcomes. Only five RCTs (10.2%) and  
80 26 ITSs (23.6%) examined microbial outcomes, most commonly colonisation or infection with resistant  
81 bacteria, or *Clostridium difficile* infection (CDI), with an explicit or implicit assumption that these would  
82 reduce. 28 (57.1%) RCTs and four (3.6%) ITSs examined all-cause mortality while length of hospital stay  
83 was measured in 15 RCTs (30.6%) and two ITSs (1.8%). However, it was often unclear whether length of  
84 stay and mortality were expected to change, and if so, in which direction (whether there was a hope  
85 that the ASI would reduce mortality and length of stay, or a fear that they would increase).

86

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

93  
94 Overall, the review authors concluded that they had found high-certainty evidence that ASI are effective  
95 in increasing compliance with antimicrobial policy and reducing duration of antimicrobial treatment, and  
96 that lower use of antimicrobials likely reduces length of stay and probably does not increase mortality.  
97 Additional trials comparing antimicrobial stewardship with no intervention are unlikely to change these  
98 conclusions. Reflecting the limited range of outcomes examined by the included studies, more research  
99 was recommended to examine the wide range of unintended consequences of restrictive interventions.

100

### 101 **What kinds of consequences should implementers of ASIs consider?**

102 There is no clear consensus on what outcomes should be measured to evaluate the impact of ASI.  
103 Professional organisations have proposed that alongside the process measures of antimicrobial use  
104 which dominate the existing literature, interventions should measure patient outcomes (mortality,  
105 length of hospital stay and readmission rates), and unintended consequences.<sup>7-9</sup> In practice,  
106 antimicrobial stewardship trialists and improvers have to make choices about what to measure given  
107 available resources. This paper describes an approach based on quality improvement work in other  
108 contexts to help plan measurement strategies in a structured way to ensure a balanced accounting of  
109 antimicrobial stewardship impact.

110

111 As with other improvement interventions, there are two prominent features of the types of measures  
112 used to evaluate effectiveness in the studies examined. These are whether outcomes are desirable or  
113 undesirable, and whether outcomes are expected or not. Of note is that for some outcomes, desirability  
114 depends on the expected direction of change (an obvious example being that *reduced* mortality is  
115 desirable, whereas *increased* mortality is undesirable), but many published papers do not clearly state  
116 their expectations before implementation. Potential metrics can therefore be divided into four main  
117 categories, any of which can be measured in terms of process and outcome, both in the clinical setting  
118 targeted by improvement and other clinical settings in which consequences might occur (for example

119 due to readmission to other services). The four type of consequences are adapted from the Diffusion of  
120 Innovations literature<sup>10-14</sup> and described in Figure 1:

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

130

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

### 132 ***ASI goals (Expected desirable consequences)***

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

138

### 139 ***ASI trade-offs (Expected undesirable consequences)***

140 Several studies pre-specified increased mortality and increased length of stay as expected undesirable  
141 consequences, with measurement intended to allow examination of trade-offs (length of stay) or  
142 provide reassurance about safety (mortality). For instance, two RCTs<sup>15 16</sup> explicitly framed length of stay  
143 and mortality as 'safety outcomes' because they were concerned that both might increase although  
144 neither actually did. Similarly, even in a context where the improvers expected their intervention to  
145 reduce length of stay, they were concerned that this might lead to higher rates of rapid readmission and  
146 measured the latter as a pre-defined trade-off.<sup>17</sup> In studies in emergency departments, some authors  
147 were concerned that prioritising rapid antimicrobial administration for patients with fever and  
148 neutropenia might compromise care for other patients. The initial measurement plans therefore  
149 included trade-offs between achieving the goals of more rapid initiation of antimicrobials and potential

150 treatment delays for patients with other urgent problems<sup>18 19</sup> and/or an expected increase in patients  
151 leaving without being seen.<sup>20</sup> In the latter study, other potential trade-offs identified before  
152 implementation included the intervention effect on nurses' workload when a febrile neutropenic patient  
153 was placed in their nursing area and the potential for staff to develop user fatigue, but the improvers  
154 chose not to explicitly measure these.<sup>20</sup>

155

### 156 ***Pleasant Surprises (Unexpected desirable consequences)***

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

167

### 168 ***Unpleasant surprises (Unexpected undesirable consequences)***

169 Only 10 studies In the Cochrane review examined unexpected or surprising negative outcomes. When  
170 outcomes are unexpected, then data have not typically been collected before and after intervention  
171 implementation, and studies most commonly examined unpleasant surprises using case-control,  
172 qualitative and cohort designs. For example, a case-control study investigating an abrupt and persistent  
173 30% increase in the absolute number of reported nosocomial infections found it was actually a pseudo-  
174 outbreak caused by physicians altering their threshold for diagnosis and reporting in response to  
175 implementation of a restrictive antimicrobial policy.<sup>26</sup> In response to a similarly restrictive intervention,  
176 qualitative interviews with clinical staff revealed unexpected difficulties with the prior approval process  
177 for restricted antimicrobials, including failure to clearly document approval and ambiguity in the  
178 duration of approval. The consequences were erosion of trust in the accuracy of feedback data about  
179 appropriate use of restricted antimicrobials.<sup>27</sup>

180

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

190  
191 Three cohort studies addressed concerns that public reporting of hospital performance on a national  
192 quality indicator of timely treatment of patients with community-acquired pneumonia (CAP) might be  
193 leading to unnecessary antibiotic treatment of patients who did not have pneumonia.<sup>32-34</sup> These  
194 concerns were supported by additional studies that were not included in the Cochrane review,<sup>35</sup> and the  
195 performance measure was subsequently revised and then withdrawn altogether.<sup>36</sup>

196  
197 One study used an ITS design to address post-implementation concerns that a change in surgical  
198 prophylaxis policy from cefuroxime to flucloxacillin plus gentamicin may have increased risk of  
199 postoperative acute kidney injury (AKI) in orthopaedic patients.<sup>37</sup> The results confirmed a clinical  
200 impression of increased AKI, and resulted in a further change to the prophylaxis policy (described in  
201 detail in Table 3 and below).

202

### 203 **Challenges associated with achieving a balanced accounting of ASI impact**

204 The framework described in Figure 1 has the benefit of bringing a systematic approach to considering  
205 the consequences of ASI, which is important because decisions often have to be made in the face of  
206 considerable uncertainty and then adapted to new information. This is illustrated by the experience of  
207 the development, implementation and modification of an ASI intended to reduce the use of surgical  
208 antimicrobial prophylaxis associated with higher risk of CDI in one Scottish Health Board (Table 3).<sup>37</sup> AKI  
209 risk was explicitly considered pre-intervention, in response to clinician concern about AKI risks in  
210 changing surgical prophylaxis to gentamicin plus flucloxacillin, and the planned intervention was  
211 amended in the patient group at highest risk of AKI (patients with fractured neck of femur). However, it  
212 was also decided that routine measurement of AKI was not required since the cost outweighed what



213 was considered a remote risk in other patients. Post-implementation, further clinical concerns that there  
214 had been increases in AKI in the lower-risk group of patients receiving gentamicin and flucloxacillin  
215 prompted rigorous investigation to quantify whether the perceived risk was real. However, the  
216 Antimicrobial Management Group (AMG) were expecting the analysis to refute the clinical concerns,  
217 and had not considered what to do if the analysis confirmed that there was a problem. When the  
218 analysis showed that gentamicin plus flucloxacillin was causing at least 10 additional cases of AKI per  
219 month in NHS Tayside, there was then a need for rapid decisions to be made with the Health Board  
220 Director of Pharmacy, Medical Director and Chief Executive about how to respond. Decision-making was  
221 complicated by the difficulties of weighing up any potential gain in lower rates of CDI against the  
222 potential harm of higher rates of AKI, but since the number of people developing AKI was approximately  
223 10 times those who might have avoided CDI as a result of the intervention, the surgical prophylaxis  
224 policy was changed to minimise AKI risk.

225

## 226 **Implications for antimicrobial stewardship programmes**

### 227 *Implications for doing and evaluating improvement*

228 Although the focus of this paper is on choice of outcomes, AMTs will also have to ensure that their  
229 evaluation design delivers results that are internally valid in terms of being as resistant to confounding  
230 and bias as possible. Although RCTs remain the ‘gold standard’ for ensuring internal validity, the  
231 Cochrane Effective Practice and Organisation of Care Group also considers trials that allocate non-  
232 randomly, controlled before-and-after studies, and ITS designs as allowing reasonable inference of  
233 causality.<sup>38</sup> In the field of AMS though, the choice for those with research funding is more likely to be  
234 between cluster-randomised controlled trials (cRCTs) and ITS designs,<sup>39</sup> (ideally controlled ITS where  
235 there is a comparison to a setting without an intervention) with ITS designs the most feasible evaluation  
236 design for clinicians and managers seeking to evaluate a local stewardship intervention.<sup>40</sup>

237

238 Assessing the full value of ASI requires a balanced accounting of the costs, risks and benefits, but  
239 assessment will often be resource constrained meaning that AMTs have to make choices about what to  
240 measure in the face of uncertainty due to the difficulty predicting how a complex, dynamic system will  
241 respond to change.<sup>10 41</sup> Before beginning or expanding a stewardship program, the AMT therefore need  
242 to plan their measurement strategy, brainstorming goals and trade-offs, articulate assumptions around  
243 the expected direction of change, and speculate on potential surprises and how they might be revealed.

244 The aim should be to identify ASI goals and likely trade-offs, and then to determine which should be  
245 measured. Indeed, many undesirable outcomes are predictable and should be accounted for from the  
246 outset. It should no longer be any surprise to an AMT that stop orders or requirements for prior  
247 approval have the potential to interrupt or delay treatment (Table 2), or that performance  
248 measurement of time to first antibiotic for patients with CAP may lead to unnecessary antibiotic  
249 treatment in patients who do not have pneumonia.<sup>35</sup> Consequently, AMTs considering an ASI using  
250 these methods should always consider if measurement of predictable trade-offs is needed,<sup>42</sup> although  
251 AMTs still need to carefully identify other likely consequences of their particular ASI in their specific  
252 context.

253  
254 Plan do Study Act (PDSA) cycles are a practical method for identifying consequences.<sup>43-45</sup> However, the  
255 application of the PDSA methodology to healthcare has often resulted in an over-simplified “Do, Do, Do”  
256 approach focused on desired *goals* at the expense of study and reflection before and after  
257 implementation, which means that improvement teams often fail to account for unexpected  
258 consequences and may not maximise benefit.<sup>46</sup> Two systematic reviews of application of PDSA methods  
259 to healthcare state that they can reveal unanticipated consequences of change but neither actually  
260 includes a detailed consideration of the full range of consequences in their data synthesis framework.<sup>45</sup>  
261 <sup>47</sup> Only one of these reviews included any information about reporting of consequences, finding that  
262 only 6 (6.4%) of 94 included studies reported “disconfirming observations” about the intervention.<sup>47</sup>

263  
264 Furthermore, the Cochrane Review identified that only a small minority of studies explicitly addressed  
265 unintended consequences, and it is notable that four (including the only RCT) were from the same  
266 institution (the University of Pennsylvania School of Medicine).<sup>18 28 29 48</sup> These studies were informed by  
267 previous research from the same hospital, which investigated the unintended effects of computerised  
268 physician orders with focus groups, interviews, shadowing and observation of house staff, nurses,  
269 information technology leaders, pharmacy leaders and attending physicians.<sup>49</sup> It is likely that this  
270 research increased awareness about unintended consequences of the ASI at this hospital. However,  
271 considering unexpected consequences should be the rule rather than the exception. An ‘improvement  
272 pause’ to take stock at a planned time after implementation will allow teams to consider whether there  
273 is enough evidence that surprises have happened to make it worth systematically measuring their  
274 impact.

275

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

289  
290 Although measurement is central to improvement, qualitative methods have much to offer in the  
291 identification of unexpected consequences to maximise benefit.<sup>10 43 44</sup> Qualitative methods can be used  
292 to help design interventions, exemplified by the Reducing Antibiotic Prescribing in Dentistry (RAPiD)  
293 study which used data about community dentists' perceptions of consequences of using surgical  
294 treatment rather than antimicrobials to design a behavioural change intervention.<sup>51</sup> Qualitative methods  
295 can also support post-implementation study and reflection. It is to be expected that clinicians will  
296 sometimes evade restrictive antimicrobial stewardship policies<sup>27</sup> in ways which are undermine the  
297 intervention, but the existence, rationale and form of workarounds can also be evidence that clinicians  
298 perceive the restriction to be difficult to safely fit into clinical workflows and that the intervention  
299 therefore needs adaptation.<sup>41 43</sup>

300  
301 ***Implications for reporting improvement interventions***  
302 The Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0) recommend that reporting of  
303 results should include “unintended consequences, such as unexpected benefits, problems, failures or  
304 costs associated with the intervention” (standard 13e).<sup>6</sup> However, the detailed explanation and  
305 elaboration document does not specifically mention this or provide an example,<sup>52</sup> and the measurement  
306 element (standard 10) focuses on process and outcome measures without specifying that these can  
307 evaluate both positive and negative consequences.<sup>6</sup> Similarly, although the Outbreak Reports and

308 Intervention studies Of Nosocomial Infection (ORION) guidelines require the reporting of any harms  
309 measured,<sup>53</sup> neither the STrengthening the Reporting of OBservational studies in Epidemiology  
310 (STROBE)<sup>54</sup> or the proposed antimicrobial stewardship extension (STROBE-AMS) reporting standards<sup>55</sup>  
311 specifically mention unintended consequences in discussion of outcomes. Irrespective of which  
312 reporting standard is most appropriate to any individual study, we recommend that reports of ASI (and  
313 other improvement interventions) should describe how the initial improvement plan was developed,  
314 including whether and how expected undesirable consequences (trade-offs) were accounted for,  
315 whether there were post-implementation surprises, and whether they were measured. Analysis should  
316 report all measured positive and negative consequences and a balanced interpretation across all  
317 measures.

### 318 **Conclusion**

319 A large proportion of the ASI reported in the literature only assess impact on their targeted process  
320 *goals* – antimicrobial prescribing – with limited examination of other potential goals including microbial  
321 and clinical outcomes. Reflecting this and the high certainty that stewardship improves prescribing in  
322 *hospitals*, the Cochrane review concluded that “future research should instead focus on measuring  
323 clinical outcomes and assessing other measures of patient safety and different stewardship  
324 interventions and explore the barriers and facilitators to implementation” (p31).<sup>5</sup> There is however less  
325 certainty about the effects of ASI in the *community*, although it will be equally important to study a  
326 balanced set of outcomes in that context.

327  
328 Achieving a balanced accounting of the impact of an ASI in both hospital and community settings  
329 requires careful consideration of expected undesirable effects (potential *trade-offs*) from the outset,  
330 and more consideration of unexpected effects after implementation (both *pleasant and unpleasant*  
331 *surprises*, although the latter will often be more important). Consensus studies to establish a core  
332 outcome set for studies of antimicrobial stewardship interventions would be useful,<sup>56 57</sup> but the  
333 proposed framework supports the systematic consideration of all consequences of improvement before  
334 and after implementation.

335

336 **Declarations**

337 **Consent for publication**

338 Not applicable

339 **Availability of data and material**

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

342 **Transparency declaration**

343 The authors declare that they have no competing interests.

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355 **from improvement science**" at the Health Foundation in London on 12<sup>th</sup> February 2016.

356

357 **Authors' contributions**

358 PD and CAM carried out the Cochrane review on which this paper draws. MT and BG were responsible  
359 for planning and leading the data extraction and analysis for this paper, and all authors contributed to  
360 analysis and interpretation. MT led the writing of the manuscript and redrafted in response to team  
361 input. BG, PD and CAM participated in critically appraising and revising the intellectual content of the  
362 manuscript. All authors read and approved the final manuscript.

363

364

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536 **Table 1: Type of outcomes measured in antimicrobial stewardship interventions**

Type of outcome measured	Randomised control trials (RCT)	Interrupted time series designs (ITS)
	No (%) (n=49)	No (%) (n=110 <sup>b</sup> )
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 <sup>a</sup> (57.1)	4 <sup>c</sup> (3.6)
Length of hospital stay	15 <sup>a</sup> (30.6)	2 <sup>c</sup> (1.8)
Other outcomes <sup>d</sup>	23 (46.9)	8 (7.2)

537 *a. 31 RCTs in total, 16 mortality only, 12 mortality and length of hospital stay, 3 length of stay only*

538 *b. 11 ITS studies included a control group for comparison*

539 *c. 6 ITS studies in total, no study included both mortality and length of hospital stay*

540 *d. Most commonly measured other outcomes included delays in starting antimicrobial treatment,*

541 *duration of fever, time spent on mechanical ventilation or increased allergic reactions*

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**Table 2: Cohort studies of unintended consequences of restrictive interventions**

Study	Restrictive intervention	Source of concern	Measures and results	Author conclusions
Connor 2007 <sup>28</sup>	Automatic stop order for vancomycin after 72h treatment. <sup>58</sup>	Stop orders may lead to inadvertent discontinuation or interruption of appropriate therapy.	Interruption of vancomycin: 1. Frequency 8% 2. Duration 6-36 hours	“Automatic stop orders are unlikely to pose a substantial risk of denying necessary antibiotic therapy to patients. These data should provide reassurance to Antimicrobial Stewardship Programmes (ASPs) that are considering instituting automatic stop orders.”
La Rosa 2007 <sup>29</sup>	A prior approval ASP that was active between 8am and 11pm. <sup>58</sup>	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). <sup>49</sup>	1. Prescribing of restricted antibiotics was 57% of total 11-12pm vs 50% 10-11pm 2. Restricted therapy continued for >1 day 65% after 11pm vs 89% before 11pm.	“Although ASPs have been shown to be beneficial, our findings reflect a potential limitation of these programmes. Further efforts to identify and correct the limitations of existing ASPs are needed to optimise their usefulness.”
Linkin 2007 <sup>30</sup>	A prior approval ASP that was active between 8am and 11pm. <sup>58</sup>	Data communicated from clinicians were found to contain inaccurate patient information in over 40% of calls made to practitioners in a prior study of this hospital’s ASP. <sup>48</sup>	Inappropriate antimicrobial therapy* with inaccurate data vs 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 2010 <sup>31</sup>	A prior approval ASP. Stat doses of restricted antimicrobials could be ordered without approval 10pm to 8am 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 vs not restricted: 1. One hour a. 8am-10pm: 46% vs 36% b. 10pm-8am: 39% vs 36% 2. Two hours or more a. 8am-10pm: 24% vs 16% b. 10pm-8am: 15% vs 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.”

\*Most common reason for rating a recommendation as inappropriate was that antimicrobial therapy was not indicated.

**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 *Clostridium difficile* infection (CDI), the Antibiotic Management Group in the 855 bedded 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.<sup>59</sup> Antimicrobial prophylaxis for orthopaedic implant surgery was changed from single dose cefuroxime 1.5g to four doses of flucloxacillin 1g plus single dose gentamicin 4mg/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 use of 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 acute kidney injury (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 postoperative AKI in orthopaedic patients from the same change in surgical prophylaxis.<sup>60</sup> In response to this concern, NHS Tayside carried out an interrupted time series 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*),<sup>37</sup> with a subsequent reduction in AKI when antimicrobial prophylaxis was changed to co-amoxiclav for all types of orthopaedic surgery.<sup>61</sup>

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% vs post-intervention 14.8%) although CDI rates in this group more than halved (3.6% vs 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 diff rates 0.8% vs 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.

**Table 4: Strategies for minimising the unintended consequences of performance measurement<sup>50</sup> and examples of studies from the Cochrane review<sup>5</sup>**

<b>Strategy</b>	<b>Examples from the Cochrane review</b>
<b>Involve staff at all levels</b>	<p>Forming inter-professional improvement teams with front line staff involving senior and junior doctors, nurses and pharmacists.<sup>20 62</sup></p> <p>Involving management at clinical service and hospital levels.<sup>20 62</sup></p> <p>Involving junior doctors<sup>63</sup> and other front line staff<sup>19 20</sup> such as pharmacists in interpreting and learning from collected data.</p>
<b>Retain flexibility in the use of performance indicators</b>	<p>Using process maps to identify performance indicators and tests of change to modify them.<sup>20 62</sup></p> <p>Using run charts to identify outliers and chart review to investigate causes and targets for change.<sup>20</sup></p> <p>Using staff coaching to identify factors contributing to performance lapses and invite suggestions for improvement.<sup>19</sup></p>
<b>Quantify every important outcome</b>	<p>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.<sup>19 20</sup> 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 beta-agonist for children with asthma).<sup>20</sup></p>
<b>Keep system under constant review</b>	<p>Specifying two or more intervention periods to allow review of consequences and adaptation of intervention.<sup>19 20 62</sup></p>

Figure 1- Types of consequences of antimicrobial stewardship interventions

