Implementation of antimicrobial stewardship interventions recommended by national toolkits in primary and secondary healthcare sectors in England: TARGET and Start Smart Then Focus

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Objectives: To assess and compare the implementation of antimicrobial stewardship (AMS) interventions recommended within the national AMS toolkits, TARGET and Start Smart Then Focus, in English primary and secondary healthcare settings in 2014, to determine the prevalence of cross-sector engagement to drive AMS interventions and to propose next steps to improve implementation of AMS.

Methods: Electronic surveys were circulated to all 211 clinical commissioning groups (CCGs; primary sector) and to 146 (out of the 159) acute trusts (secondary sector) in England. Response rates were 39% and 63% for the primary and secondary sectors, respectively.

Results: The majority of CCGs and acute trusts reported reviewing national AMS toolkits formally or informally (60% and 87%, respectively). However, only 13% of CCGs and 46% of acute trusts had developed an action plan for the implementation of these toolkits. Only 5% of CCGs had antimicrobial pharmacists in post; however, the role of specialist antimicrobial pharmacists continued to remain embedded within acute trusts, with 83% of responding trusts having an antimicrobial pharmacist at a senior grade.

Conclusions: The majority of healthcare organizations review national AMS toolkits; however, implementation of the toolkits, through the development of action plans to deliver AMS interventions, requires improvement. For the first time, we report the extent of cross-sector and multidisciplinary collaboration to deliver AMS interventions in both primary and secondary care sectors in England. Results highlight that further qualitative and quantitative work is required to explore mutual benefits and promote best practice. Antimicrobial pharmacists remain leaders for implementing AMS interventions across both primary and secondary healthcare sectors.

Introduction

Antimicrobial resistance (AMR) poses a major threat to healthcare globally, having clinical, social and economic implications.1,2 The use and inappropriate use of antimicrobials is a recognized driver of drug-resistant infections.3 Patients with infections due to resistant organisms may experience delayed recovery or treatment failure, increased hospital stay and increased mortality.4

Interventions to reduce inappropriate antimicrobial prescribing can reduce AMR or healthcare-acquired infections, and interventions to increase effective prescribing are important in improving patient safety clinical outcomes.5 Antimicrobial stewardship (AMS) programmes in clinical settings utilize evidence-based guidelines, educational activities and regular feedback of antibiotic usage data to prescribers to promote rational prescribing.1,3 In the UK, a cross-government 5 year strategy to tackle antimicrobial resistance was published in 2013.3 The strategy outlines seven key areas for action, one of which is the optimization of prescribing practice through implementation of AMS programmes.
AMS toolkits for England are freely and openly available to assist organizations to fulfil their obligations with regard to national guidance and regulations. These toolkits are Treat Antibiotics Responsibly, Guidance, Education, Tools (TARGET) for primary care, and Start Smart Then Focus (SSTF) for secondary healthcare settings.10,11

TARGET

The TARGET toolkit was launched by PHE and the Royal College of General Practitioners in November 2012. TARGET resources include guidance (local or national antibiotic treatment recommendations), educational materials and tools that general practitioners (GPs) can share with patients during consultations (including information on expected duration of infection, self-care and back-up prescriptions) and suggested antibiotic practice audits. The TARGET materials were updated in 2013 following user testing and evaluations.

SSTF

SSTF was first published in November 2011.11,12 Proof of adherence to SSTF AMS principles helps organizations to demonstrate compliance with The Health and Social Care Act 2008: Code of Practice on the Prevention and Control of Infections and Related Guidance (updated in 2015).13 The Code of Practice states that registered providers should demonstrate ‘Systems to manage and monitor the prevention and control of infection’ and ‘Ensure appropriate antimicrobial use to optimise patient outcomes and to reduce the risk of adverse events and antimicrobial resistance’.13

SSTF recommends that, as a minimum, providers should develop an action plan and monitor adherence to AMS principles regularly in all clinical areas at least annually, including evidence of clinical indication and treatment duration (or review date) documented on the drug chart, and review of antibiotics at 48–72 h after initiation and documentation of the antimicrobial prescribing decision on the drug chart or in the clinical notes. It also highlights the importance of local guidance for treatment of common conditions based on local antibiotic resistance epidemiology.

Aim

This study aimed to assess and compare the implementation of AMS interventions recommended by national AMS toolkits in English primary and secondary care settings, to determine the prevalence of cross-sector engagement to drive AMS interventions, and to propose next steps to improve implementation of AMS.

Methods

Two web-based cross-sectional studies, one for primary care and the other for secondary care (available as Supplementary data at JAC Online), were developed and deployed using PHE’s Select Survey programme to assess the implementation of AMS interventions recommended by the TARGET and SSTF toolkits. Questions within both surveys were informed by published AMS guidance and designed to build on previous surveys. Both surveys were piloted in smaller cohorts [10 clinical commissioning groups (CCGs) and 18 National Health Service (NHS) acute trusts], and revised prior to national circulation.

CCGs are independent statutory bodies governed by members of local general practices with support from health professionals and direct input from people representing patients and members of the public. CCGs have a legal duty to support quality improvement in general practice. All 211 CCGs in England were invited by e-mail to complete the primary care survey as part of activities for European Antibiotic Awareness Day (EAAD) in November 2014.

CCGs are also responsible for commissioning secondary (hospital) and community care services for their local geographies. In England, NHS secondary health services are provided by acute trusts, which may consist of one or more hospitals. The secondary care survey was distributed nationally to antimicrobial pharmacists in 92% of acute trusts in England (146/159) in May 2014; this was due to incomplete contact details for antimicrobial pharmacists in all trusts following altered clinical delivery in England.

Not all questions were answered by all responding CCGs and acute trusts. Where the question was not answered by all responders (82 CCGs and 100 NHS acute trusts), the total number of responses (n) for these questions is provided.

These surveys were voluntary service evaluations completed by healthcare professionals and thus ethics approval was not required. Survey responses were analysed using Stata (version 13) and Microsoft Excel. ORs were calculated using logistic regression with the implementation of an action plan as the outcome variable to determine the impact of reviewing AMS toolkits.

Results

Of 82 responding CCGs, 25% had 0–25 member general practices, 41% contained 26–49 general practices, 26% contained 50–74 general practices, 6% contained 75–99 general practices and 2% contained ≥100 general practices. Twenty-eight responding acute trusts were teaching hospitals. The mean number of hospital sites per acute trust was 2 (range 1–5); 27% of acute trusts had <500 beds, 51% had 500–999 beds and 22% had ≥1000 beds.

Implementation of the national AMS toolkits

Of the responding CCGs, 60% had formally or informally reviewed TARGET and 13% had an action plan to implement AMS interventions recommended by TARGET (Table 1). CCGs that had either formally or informally reviewed TARGET were over eight times more likely to have implemented an action plan (OR 8.68, 95% CI 1.06–71.48, P = 0.044), and four times more likely to have implemented the use of the TARGET patient information leaflet (OR 4.38, 95% CI 1.70–11.27, P = 0.002) compared with those that had performed no review. Acute trusts that had undertaken a formal or informal review of SSTF were over three times more likely to have implemented an action plan compared with those that had not performed any review (OR 3.33, 95% CI 1.00–11.06, P = 0.050).

AMS interventions recommended by national AMS toolkits

Key AMS interventions recommended in TARGET and SSTF toolkits are the provision of an AMS committee, a written dedicated antimicrobial policy, a written education and training strategy and the implementation of audits within these AMS toolkits. We report the implementation of each key AMS activity within primary and secondary healthcare below.

Existence of an AMS committee

Fifteen CCGs (18%) reported having a specific AMS committee (Table 1); however, the AMS role in CCGs was reported to be
of the 94 (94%) acute trusts with AMS committees (Table 1); 99% kept minutes, 92% had terms of reference and 87% drafted lists of actions as per the recommended

<table>
<thead>
<tr>
<th>Table 1. Implementation of AMS interventions recommended by national AMS toolkits by CCGs and NHS acute trusts</th>
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<tr>
<td>Percentage of acute trusts (n=159 at time of survey)</td>
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<tr>
<td>---------------------------------------------------------------</td>
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<tr>
<td>Proportion of responses received</td>
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<tr>
<td>Proportion of NHS area teams represented in survey responses</td>
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<thead>
<tr>
<th>Implementation of national AMS toolkits</th>
<th>Percentage of acute trusts (n=159 at time of survey)</th>
<th>Percentage of CCGs (n=211 at time of survey)</th>
</tr>
</thead>
<tbody>
<tr>
<td>formally or informally reviewed national AMS toolkits</td>
<td>87</td>
<td>60</td>
</tr>
<tr>
<td>implemented an action plan to deliver national toolkit AMS interventions</td>
<td>46</td>
<td>13</td>
</tr>
<tr>
<td>implemented use of TARGET patient information leaflet</td>
<td>NA</td>
<td>50</td>
</tr>
<tr>
<td>using TARGET educational presentation within the CCG</td>
<td>NA</td>
<td>59</td>
</tr>
<tr>
<td>promote TARGET during practice prescribing visits, where prescribing advisers visit the GP practice</td>
<td>NA</td>
<td>58</td>
</tr>
<tr>
<td>promoted use of TARGET to GPs for use in CPD/revalidation</td>
<td>NA</td>
<td>46</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AMS committee</th>
<th>Percentage of acute trusts (n=100)</th>
<th>Percentage of CCGs (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>existence of an AMS committee dedicated to reviewing antimicrobial use</td>
<td>94</td>
<td>18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Written dedicated antimicrobial policy</th>
<th>Percentage of acute trusts (n=100)</th>
<th>Percentage of CCGs (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>have guidelines and/or a policy for antibiotic prescribing</td>
<td>93</td>
<td>99</td>
</tr>
<tr>
<td>use of a restricted antibiotics list for empirical prescribing</td>
<td>83</td>
<td>73</td>
</tr>
<tr>
<td>use of an intravenous to oral switch policy</td>
<td>82</td>
<td>NA</td>
</tr>
<tr>
<td>use of an automatic stop policy</td>
<td>19</td>
<td>NA</td>
</tr>
<tr>
<td>use of a separate antimicrobial drug chart/section</td>
<td>59</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AMS audits</th>
<th>Percentage of acute trusts (n=100)</th>
<th>Percentage of CCGs (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>implemented AMS audits suggested by audit plans within national AMS toolkits</td>
<td>74</td>
<td>15</td>
</tr>
<tr>
<td>or collated data as part of organization-wide point prevalence surveys</td>
<td></td>
<td></td>
</tr>
<tr>
<td>an audit of adherence to guidelines (dose, route and duration) is implemented within the audit plan or already collated as part of an organization-wide point prevalence survey</td>
<td>82</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Education and training</th>
<th>Percentage of acute trusts (n=100)</th>
<th>Percentage of CCGs (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>has a written antimicrobial education and training strategy</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>competency assessments carried out for prescriber</td>
<td>17</td>
<td>NA</td>
</tr>
<tr>
<td>competency assessments are mandatory</td>
<td>20</td>
<td>NA</td>
</tr>
<tr>
<td>all doctors on induction receive antibiotic guidelines</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>all doctors on induction receive antibiotic guidelines and a lecture/in-person training on antimicrobial prescribing</td>
<td>63</td>
<td>15</td>
</tr>
<tr>
<td>all doctors on induction receive antibiotic guidelines and need to do an e-learning module on antimicrobial prescribing</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>teaching on induction for all nurses</td>
<td>27</td>
<td>6</td>
</tr>
<tr>
<td>teaching on induction for all pharmacists</td>
<td>69</td>
<td>6</td>
</tr>
<tr>
<td>teaching on induction for non-medical prescribers</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>mandatory e-learning for senior doctors (registrar and higher)</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>mandatory e-learning for junior doctors</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>AMPS training is left to individual trainers to decide</td>
<td>NA</td>
<td>33</td>
</tr>
</tbody>
</table>

NA, question not asked; CPD, Continuing Professional Development.
governance structure reporting to the IPC committee or equivalent.

Membership of acute trust AMS committees was diverse, with some specialties being more commonly represented than others (Figure 1). Microbiologists and specialist antimicrobial pharmacists were the most common specialists on acute trust AMS committees, whereas representation from nurses, physicians, surgeons, intensivists, paediatricians, junior doctors, anaesthetists and primary care (CCG) representatives was low.

Written dedicated antimicrobial policy

Details of antimicrobial policies within primary and secondary care are presented in Table 1. Ninety-four (94%) and 93 (93%) of responding acute trusts reported having an antimicrobial formulary and empirical guidance in place, respectively. Antimicrobial policies were updated yearly by 30% of acute trusts, every 2 years by 45% of acute trusts, every 3 years by 16.5% of acute trusts or at intervals of ≥4 years by 2% of acute trusts. Five point five percent of acute trusts reported updating their antimicrobial policies more regularly than once per year and 1% of acute trusts reported never updating their antimicrobial policy (n=91).

AMS audits

Few CCGs had implemented suggested AMS audits within the TARGET audit plan or collated data as part of CCG-wide point prevalence surveys (Table 1); however, 53 (69%) responding CCGs had used local antibiotic audits within the past 2 years. Implementation of AMS audits within the TARGET audit plan was associated with the promotion of TARGET during practice prescribing visits (P=0.03) and with formal or informal review of TARGET (P=0.03).

Eighty-four percent of acute trusts conducted a trust-wide antimicrobial point prevalence survey at least annually and 2% of acute trusts reported never conducting one (n=89). The majority of respondents collated data for at least one of the AMS audits suggested by SSTF within the trust audit plan or as part of trust-wide antimicrobial point prevalence surveys. The most frequent recommended SSTF audits in trust-wide point prevalence surveys included: adherence to guidelines of dose, route and duration (82%); clinical indication and treatment duration documented on drug chart (82%); and intravenous to oral switch at 48 h (49%). Other audits, such as review of prescription/evidence of documenting decision at 48 h and time to first dose in severe sepsis, were less commonly implemented (42% and 40% of acute trusts, respectively).

Education and training strategies

The implementation of education and training initiatives in primary and secondary care varied, as shown in Table 1.

Additional key aspects of implementing AMS

The role of specialists in leading AMS interventions

In primary care, prescribing advisers/medicine management pharmacists led the AMS and prescribing strategy in 54 (66%) responding CCGs, whereas only 4 (5%) CCGs had a specialist antimicrobial pharmacist undertaking this role. This role was also undertaken by quality or nursing clinical leads (6%) or by general practice clinical leads (2%).

The secondary care survey showed that 94 (94%) responding acute trusts had at least one specialist antimicrobial pharmacist

Figure 1. Membership of AMS committees in NHS acute trusts, England, 2014.
or pharmacy technician in post, confirming the continuing importance of this role. The number of these posts per acute trust ranged from 0 to 3 with an average of 1.4. Pharmacy technicians (band 5 or higher) and band 7 pharmacists were found in 2 (2%) and 9 (9%) acute trusts, respectively. Band 8a pharmacists were embedded within 59 (59%) acute trusts. Pharmacists at bands 8b and 8c were found in 17 (17%) and 2 (2%) acute trusts, respectively. Consultant pharmacists were employed in 5 (5%) acute trusts. These posts are usually, but not exclusively, band 8c and above.

Survey responses demonstrated that specialist antimicrobial pharmacists in secondary care had an extensive role, which included: writing antimicrobial guidelines and policies in 96 (96%) acute trusts; making anti-infective formulary decisions, i.e. choosing which antimicrobials should be available on the trust formulary (91%); being available by phone or pager for referrals (91%); performing multi-disciplinary antibiotic review rounds (90%); and attending trust IPC committee meetings (89%). Horizon scanning (70%), attending ward rounds on specialties with high antibiotic use (64%) and maintaining awareness of local resistance patterns (53%) were aspects of fewer specialist antimicrobial pharmacist roles.

Cross-sector AMS

Cross-sector AMS is the collaboration of different healthcare sectors and specialities, working together to deliver AMS across the whole healthcare economy. The secondary care survey collated data on collaboration between CCGs and acute trust colleagues on the development of antimicrobial guidelines and stewardship interventions across both sectors. Thirty-five (35%) acute trust respondents had a working relationship with primary care colleagues in their area and were able to provide a named contact.

In order to deliver AMS, 73 (89%) responding CCGs worked collaboratively with an acute trust clinician such as a microbiologist, 71 (87%) with general practices, 62 (76%) with community service providers and 45 (55%) with community pharmacies. As shown in Table 2, the proportion of CCGs and acute trusts that participated in the production of joint AMS-related materials and training was low.

**Table 2. Joint AMS-related materials or training being produced by CCGs in collaboration with acute trusts**

<table>
<thead>
<tr>
<th>AMS-related materials or training produced in collaboration with acute trusts</th>
<th>Percentage of CCGs (n=82)</th>
</tr>
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<tbody>
<tr>
<td>Joint anti-infective guidelines/policies</td>
<td>54</td>
</tr>
<tr>
<td>Joint anti-infective formulary</td>
<td>48</td>
</tr>
<tr>
<td>Joint anti-infective education for doctors</td>
<td>23</td>
</tr>
<tr>
<td>Joint anti-infective education for nurses</td>
<td>21</td>
</tr>
<tr>
<td>Joint anti-infective education for other healthcare professionals</td>
<td>15</td>
</tr>
</tbody>
</table>

Regarding future plans for primary-secondary sector collaboration, 39 (48%) responding CCGs reported that they did not know of any plans to develop cross-sector stewardship interventions with acute trusts. Thirty-four (41%) reported that they would collaborate with acute trusts on cross-sector AMS within the following 1–2 years. Nine (11%) CCGs stated that they had no such future plans.

**Discussion**

Results of our surveys demonstrate that formal or informal review of national AMS toolkits was a strong predictor of the implementation of the toolkits and development of a corresponding AMS action plan in primary and secondary healthcare sectors in England. Implementation of the national AMS toolkits has led to a number of actions to improve AMS activity; however, the results demonstrate that implementation has not been universal, with some interventions being conducted more commonly than others.

Fifteen percent of responding CCGs had implemented suggested AMS audits within the TARGET audit plan or collated data as part of CCG-wide point prevalence surveys; however, the majority of CCGs (69%) implemented their own independent antibiotic audits.

While 74% of acute trusts collated data on at least one of the recommended audits in SSTF, audits related to ‘starting smart’, such as documentation of dose and duration, were more commonly implemented than those relating to ‘then focus’ aspects of AMS (e.g. evidence of 48 h review). These findings support those by Llewellyn et al., who found that policies in 100/105 acute trusts (95%) recommended antimicrobial prescription reviews, but only 46/96 respondents (48%) reported monitoring compliance. Effective implementation of ‘focus’ aspects of AMS guidance, such as interventions to increase the frequency and effectiveness of post-prescription reviews, could help to reduce unnecessarily broad-spectrum and prolonged antibiotic therapy.

Components of antimicrobial policies in secondary care have remained consistent from 2011 to 2014. However, two significant changes are important to highlight: fewer acute trusts reported utilizing an automatic stop policy (from 36% to 19%) and the number of acute trusts with a separate antimicrobial drug chart section had increased (from 32% to 59%). It is likely that separate antimicrobial sections/drug charts for antimicrobials reduced the need for automatic stop policies. Assessment of individual trust responses revealed that those without an automatic stop policy had a separate antimicrobial section/drug chart whereby only 7 days of antibiotic prescription could be dispensed.

A multidisciplinary committee is recommended to provide an active and collaborative approach to AMS. In primary care AMS was more likely to be overseen by a drugs and therapeutics committee than a dedicated AMS committee. Further investigation is required to determine whether these alternative committees are as effective in delivering AMS interventions and improved antibiotic prescribing outcomes as dedicated committees or groups.

Whilst >90% of responding acute trusts had a dedicated AMS committee as recommended by SSTF, this survey showed that representation of specialities varied. Participation from general pharmacists, anaesthetists, surgeons, junior doctors, paediatricians, nurses, physicians and primary care representation was low (Figure 1).

Key area 3 within the UK 5 year AMR strategy is ‘improving professional education, training and public engagement to improve clinical practice and promote wider understanding of the need for more sustainable use of antibiotics’. There was high availability
of clinical guidelines to promote appropriate prescribing in both primary and secondary care. The presence of a written antimicrobial education and training strategy was low in both primary and secondary healthcare sectors. Teaching specifically about antibiotics was more common for doctors and pharmacists than for nurses starting work in acute trusts, a trend mirrored globally. Over one-third of antimicrobial prescribing and stewardship training conducted in CCGs was decided by individual CCG trainers. This may have led to inconsistency, resulting in low levels of education and training initiatives implemented by CCGs. The first national antimicrobial prescribing and stewardship (AMPS) competences were published in 2013. The competences are an integral resource to help organizations develop training materials to educate professionals regarding AMS.

Given the move towards integrated care, the fact that at least 85% of CCGs had some method of interaction with acute trusts was encouraging. However, just 55% of CCGs worked with community pharmacies to deliver AMS. Community pharmacists have a key role in educating the public on optimal antibiotic use. A study conducted by community pharmacists stated that almost all the patients interviewed would preferentially attend a pharmacy for management of their urinary tract infection symptoms due to ‘convenience, difficulties obtaining a GP appointment, and reluctance to trouble GPs with a non-emergency problem’. Therefore developing cross-sector AMS with community pharmacies is expected to be beneficial.

In primary care, prescribing advisers or medicines management pharmacists were more likely to lead AMS interventions; in the few instances where specialist antimicrobial pharmacists fulfilled this role, more time was dedicated to AMS. The role of specialist antimicrobial pharmacists continues to remain embedded within acute trusts, with the majority having a specialist pharmacist for antimicrobials or infection management at NHS staff grading ‘Agenda for Change’ (AFC) band 8a (Advanced Pharmacist) and above in post. In addition, the antimicrobial pharmacist role spanned a broad range of specialist activities. It is essential that the important role of these specialist pharmacists continues to be recognized following the initial central funding provided in 2003.

Pharmacists as a whole are the most engaged professional group in conveying the risks of AMR to the public as part of England’s activities for EAAD. This is a crucial activity as increasing knowledge and awareness of AMR within the general public is likely to decrease inappropriate demand, thus enabling the public to play their part in AMS.

**Limitations**

The survey was not sent to 100% of acute trusts because contact details of antimicrobial pharmacists were unavailable due to recent changes in healthcare organizational structures. The high response rate from both teaching and non-teaching NHS acute trusts across all English regions allows these findings to be generalizable across the NHS. In contrast, the lower (39%) response rate from CCGs limits the generalizability of the statements in primary care. These surveys did not include responses from prescribers, drug administrators (predominantly nurses) and non-specialist pharmacists. Further mixed-methods investigation of practice is required to understand the behaviour of healthcare workers in relation to AMS.

**Next steps**

Since the completion of this study SSTF has been updated in light of newly published evidence and user feedback. NICE has recently published a guidance on ‘Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use’, which highlighted TARGET and SSTF as resources for organizations and health professionals to improve the quality of antimicrobial prescribing and reduce the emergence of resistance in healthcare settings. It is important that those who commission and regulate NHS services assess AMS interventions in the practices and organizations they review. In addition, PHE needs to continue to work with professional organizations and Health Education England (HEE) to disseminate information about these resources so as to improve their uptake. A level 2 patient safety alert to raise awareness of AMS toolkits and AMPS competencies among clinical leaders was published jointly by NHS England, PHE and HEE in August 2015. Potential barriers to and the feasibility of adopting cross-sector AMS implementation should be explored, as the majority of CCGs who responded to our survey had no plans or were unaware of any plans for their CCG and local acute trusts to develop cross-sector stewardship. Further quantitative and qualitative work is required to best describe the key components and essential elements of AMS committees to lead to effective behaviour change and improved prescribing practice in modern healthcare.

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Disclaimer
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Supplementary data
Both the primary and secondary healthcare sector surveys are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References