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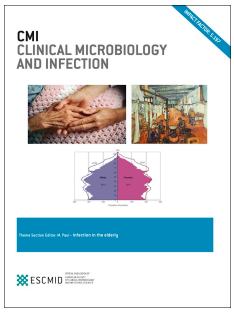

Prioritising research areas for antibiotic stewardship programmes in hospitals: a behavioural perspective consensus paper

Magdalena Rzewuska, Esmita Charani, Janet E. Clarkson, Peter G. Davey, Eilidh M. Duncan, Jill J Francis, Katie Gillies, Winfried V. Kern, Fabiana Lorencatto, Charis A. Marwick, Jo McEwen, Ralph Möhler, Andrew M. Morris, Craig R. Ramsay, Susan Rogers Van Katwyk, Brita Skodvin, Ingrid Smith, Kathryn N. Suh, Jeremy M. Grimshaw

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Prioritising research areas for antibiotic stewardship programmes in hospitals: a behavioural perspective consensus paper

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Running title: Consensus on research priorities for antibiotic stewardship programmes in hospitals

Key words: antimicrobial stewardship; research priorities; nominal group technique; multidisciplinary approach; behavioural approach

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Abstract

Scope

Antibiotic stewardship programmes (ASPs) are necessary in hospitals to improve the judicious use of antibiotics. While ASPs require complex change of key behaviours on individual, team, organisation and policy levels, evidence from the behavioural sciences is underutilised in antibiotic stewardship studies across the world, including high-income countries (HICs). A consensus procedure was performed to propose research priority areas for optimising effective implementation of ASPs in hospital settings, using a behavioural perspective.

Methods

A workgroup for behavioural approaches to ASPs was convened in response to the fourth call for leading expert network proposals by the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR). Eighteen clinical and academic specialists in antibiotic stewardship, implementation science and behaviour change from four high-income countries with publicly-funded health care systems (that is Canada, Germany, Norway and the UK), met face-to-face to agree on broad research priority areas using a structured consensus method.

Question addressed and recommendations

The consensus process on the 10 identified research priority areas resulted in recommendations that need urgent scientific interest and funding to optimise effective implementation of antibiotic stewardship programmes for hospital inpatients in HICs with publicly-funded health care systems. We suggest and detail, behavioural science evidence-guided research efforts in the following areas: 1) Comprehensively identifying barriers and facilitators to implementing antibiotic stewardship programmes and clinical recommendations intended to optimise antibiotic prescribing; 2) Identifying actors ('who') and actions ('what needs to be done') of antibiotic stewardship programmes and clinical teams; 3) Synthesising available evidence to support future research and planning for antibiotic stewardship programmes; 4) Specifying the activities in current antibiotic stewardship programmes with the purpose of defining a 'control group' for comparison with new

initiatives; 5) Defining a balanced set of outcomes and measures to evaluate the effects of interventions focused on reducing unnecessary exposure to antibiotics; 6) Conducting robust evaluations of antibiotic stewardship programmes with built-in process evaluations and fidelity assessments; 7) Defining and designing antibiotic stewardship programmes; 8) Establishing the evidence base for impact of antibiotic stewardship programmes on resistance; 9) Investigating the role and impact of government and policy contexts on antibiotic stewardship programmes; and 10) Understanding what matters to patients in antibiotic stewardship programmes in hospitals.

Assessment, revisions and updates of our priority-setting exercise should be considered, at intervals of 2 years. To propose research priority areas in low- and medium income countries (LIMCs), the methodology reported here could be applied.

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Scope

The proposed overarching priority research areas are intended for researchers, representatives from funding agencies and policy-makers. These priorities provide suggestions on what needs urgent scientific interest and funding to optimise effective implementation of antibiotic stewardship programmes for hospital inpatients using theoretical and empirical evidence from behavioural sciences. We based those suggestions on experiences from high-income countries (HICs) with publicly-funded health care systems, where most evidence on antibiotic stewardship come from.

Context

Antibiotic resistance is a globally important problem associated with excess mortality, morbidity, prolonged hospital stays and increased healthcare costs [1]. Overuse or inappropriate use of antibiotics drives the development of antibiotic resistance [2]. The vast majority of human consumption of antibiotics occurs in primary-care settings and nursing homes [3], but antibiotic resistance has predominantly been a clinical problem in hospitals which are particularly susceptible to harbouring multidrug-resistant organisms [4]. Therefore, antibiotic stewardship is essential to improve the judicious use of antibiotics in hospitals by providing practitioners with tools to prescribe effective therapy while reducing antibiotic-related adverse events, such as antibiotic resistance [1,4].

An antibiotic stewardship programme (ASP) is a coherent set of collective daily actions that promotes using antibiotic agents responsibly, where 'action' is defined as a strategy (*i.e.* a specific set of coherent interventions) [5]. In practice, ASPs involve a heterogeneous group of system- and organisation-based actions, so understandably there is not only substantial transnational variability in the development and implementation of ASPs [6], but even organisation-level variability in HICs [7-10]. This suggests a global need to optimise and standardise the implementation of ASPs. Co-ordinated transnational response efforts are underway to enhance the implementation (*i.e.* uptake into practice and policy) of effective ASPs [4]. The planning of such large-scale quality improvement initiatives first requires optimising the use of existing research resource management [11]. The

growing number of research projects on ASPs being conducted and submitted for publication demonstrates that it is a priority area [12], but a number of important research gaps still need to be addressed [4]. Addressing high-importance questions (*i.e.* research priorities) will reduce avoidable research waste [11]. Core elements and checklist items for global ASPs, including in LIMCs where most of antibiotics are prescribed, have been developed [13], but without a behavioural 'lens'. More robust qualitative research investigating contextual influences on ASPs is needed from LMICs to propose research priorities for those countries using behavioural 'lens'.

An antibiotic stewardship programme requires complex behaviour change; multiple healthcare providers are required to change multiple behaviours at different time points in the patient care pathway. Moreover, change is required at the individual, team, organisation and policy levels to change key behaviours. It has been widely recognised that evidence from behavioural science can be used to inform that change [3,4,14,15]. The underlying principle of this need is understanding the difference between recommendations for appropriate antibiotic use (the 'what') and behaviour change interventions (the 'how') [3]. To inform the development of a more effective health behaviour change intervention (that is a systematic interference designed to modify how an individual acts), researchers have started to specify the active ingredients of interventions in terms of their component behaviour change techniques (BCTs) [16]. BCTs are the observable, replicable components of behaviour change interventions. We know from a Cochrane review that interventions to improve the translation of antibiotic use recommendations into practice are effective in increasing compliance with antibiotic policy and reducing duration of antibiotic treatment in acute care hospital settings [14]. However, the review suggests that few of those interventions used effective behaviour change techniques (such as action planning or feedback), the role of a key stakeholder (*i.e.* junior doctors) is mostly overlooked, and interventions are developed at the local level on an *ad hoc* basis [14]. One of the main recommendations from the review included a need to bring together world experts in antibiotic stewardship in partnership with experts in implementation and social sciences to develop a research agenda to guide future research efforts to optimise effective implementation of ASPs in hospital settings [14].

Question addressed

What are the research priority areas to optimise effective implementation of ASPs in hospital settings in HICs with publicly-funded health care systems?

Methods

Description of the development group

A transnational multidisciplinary workgroup on behavioural approaches to ASPs was convened in response to the fourth call for leading experts' network proposals of the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR). The steering committee (CR, JMG, PGD) identified 16 members (all the other co-authors) through a process of peer knowledge sharing and consultation, through existing research networks and contacts. Members were invited on the basis of: 1) their recognized expertise in antibiotic stewardship, behavioural and implementation science, including clinical leads, senior academic staff or experts for health authorities or policy-makers, with at least 10 years of experience in their subject area or 2) being frontline clinical staff, clinical- academic or non-clinical academic staff with extensive experience in the above three areas and 3) coming from a high-income countries with publicly funded health care systems. In total, the group included 19 members from the UK (11), Germany (2), Norway (2) and Canada (4). The members had different backgrounds, including infectious disease physicians, nurses, researchers; implementation scientists; health psychologists; intervention design methodologists and health care service scientists (full list: Appendix 1- Supplementary materials 1).

Consensus procedure

The workgroup met face-to-face on the 27th - 28th April 2017 (in Birmingham, UK) and 30th- 31st October 2017 (in Aberdeen, UK). Meetings were audio-recorded and summarized and notes were taken. To ensure the priority-setting team had necessary information about the context [17], each meeting was guided by an agenda for activities, including practical group work and presentations of knowledge synthesis undertaken by the workgroup. The latter included: a non-systematic review and knowledge synthesis of existing evidence on ASP implementation efforts worldwide; a systematic review of multi-country studies on barriers and facilitators

to ASPs in hospitals (PROSPERO registration number CRD42017076425); and the Cochrane review of interventions to improve antibiotic prescribing to hospital inpatients [14].

The stages of the priority setting process were informed by existing literature [18] and are summarised in Figure 1. We used the nominal group technique (NGT) - a commonly used formal consensus development method involving a highly structured face-to-face group interaction. Practical benefits for which we chose the NGT included: immediate dissemination of results to the group [19], giving equal voice to each participant by encouraging individual input [19], reduction of personality effects (*e.g.* influences of a power structure) and creating an environment conducive to initiation of change [20]. In our experience research needs within the area of behavioural approaches to ASPs are vast and intertwined. Also, in practice, specific research questions are likely to vary across systems and specific settings [8]. Therefore, similar to Healy and colleagues [21], we used a modified James Lind Alliance (JLA) process [22] that led to suggesting unique broad general prioritisation research areas rather than specific research questions.

The process protocol is presented in the Supplementary Materials 1. . The session began the workgroup coordinator (CR) with an introduction to the whole group and an explanation of the purpose of the activity. Participating members then split into two equal-sized groups. Each group was allocated one consensus decision-making process facilitator (KG and EMD). Both have been previously involve in a consensus process, and one facilitator (KG) also had previous experiences with the JLA process. We selected facilitators with the skills to unite differing perspectives and spheres of expertise and enabling interaction [23]. To capture experiential differences in people with similar background, thereby giving rise to new perspectives, participants with similar areas of expertise were grouped together (*e.g.* experts in infectious diseases and health psychology and implementation). At the same time, to stimulate discussion, each group included sub-groups with at least three different areas of expertise and we also included a clinical-academic in each group. Participants were asked to generate specific research ideas in these groups. For this purpose, in silence, participants wrote down research ideas on provided sticky notes. They were instructed to write one idea per note and encouraged to use

as many notes as needed. Each participant presented and brought their research ideas forward for discussion in their groups by reading them aloud and explaining their choices. All ideas were collected, numbered and displayed on a flipchart board by a group facilitator. All participants were then asked to read the ideas generated by the other group.

Participants were brought together through discussion and inductively collated overlapping research ideas into topics. In the JLA process of priority setting – a well-established framework – typically the main focus is to agree the list of the Top 10 priorities for future research [22]. However, to avoid artificial consensus, the group was not informed about this specific number. Instead, we planned to offer the group an option to decide how many research priority topics would be carried forward for ranking and prepared *a priori* a strategy to reduce the number of generated topics if necessary (detailed in the Supplementary Materials 1).

After a short break, each participant was provided with a printed copy of the prioritised research topics and asked to rank these priorities from most to least important. An e-polling system that collects and summarises responses was used to collate the ranking of the priority ideas. Responses were submitted using personal electronic devices. After an interval for another activity, the results were presented to the group on a large projection screen. A facilitator then guided the participants through listening to each idea, opinion, and concern and initiated discussion to reach consensus (*i.e.* a solution that everyone actively supports, or at least can accept).

Results

Consensus process

The consensus process for research priority setting took place in Aberdeen in October 2017 and lasted 2.5 hours. Sixteen members generated and collated research ideas into topics, of which fifteen (one person had to leave an activity early) ranked the prioritised research topics. Following discussion, the group spontaneously collated individually-generated overlapping research ideas into 10 research topics, hence there was no need to consider reducing the numbers of generated topics. During the discussion of the results of ranking of the prioritised research topics, the group concluded that the top five research priorities received similar ranking scores;

priority research areas are inter-dependent, and so research is much needed across all ten.

The dynamic of each group was different, due to different personalities, experiences, expertise, backgrounds, communication styles and levels of confidence. The discussions were however vigorous and each participant took strong ownership of their own proposed ideas. The presence of a facilitator, with experience in both behavioural and implementation science, to moderate those discussions ensured mutual understanding. Placing individuals with similar background and prior presentations and group activities also facilitated shared understanding. In the next step, pragmatism was required to collate individual research ideas to reach acceptable compromises and revision of opinions in the search for consensus. At this point, the group required the assistance of the second facilitator and an administrator for record keeping, to ensure full, fair, respectful and equal participation.

Recommendations

Table 1 shows priorities and ranked research topics grouped into three main descriptive themes. Individual research ideas are presented in the Supplementary Materials 2. We would anticipate research teams to select the broad research areas prioritised and develop a specific research project from them. For example, one research objective for the top research priority would be: *Developing a core outcome set, reflecting clinicians' and patients' views, to enable evaluation of effectiveness of an intervention to support behaviour change, specified (in terms of Target, Action, Context, Time, Actor (TACTA)), focused on reducing unnecessary exposure to antibiotics in hospital patients.* Within the second top research priority topic, a specific research objective could be*: Developing and piloting a multicentre, transnational, cluster-randomised controlled trial to compare short- and long-term effects of two ASPs with different BCT-specified antibiotic stewardship interventions in hospital inpatient settings.* An example research objective within the third research topic: *Estimating short- and long-term effects of TACTA-specified ASP behaviours on Gram-negative and Gram-positive bacteria, using a controlled interventional study design and data-reporting*.

Implications

The main implication of this consensus work is potentially reducing avoidable waste and inefficiency in research by directing future research to address the proposed uncertainties of importance [23]. To facilitate this process, participation of a priority-setting team in discussion with the community of interest, to share findings and experiences, is recommended [17]. Research teams are encouraged to identify opportunities for building robust proposals focused on comprehensively addressing research objectives within these priorities. Robust proposals could be informed by recommendations for avoiding research waste [11]; and guidance on designing and reporting of ASP intervention studies [24,25], implementation studies [26] and behaviour change interventions [27,28]. ASPs are a global concern, and hence best addressed by engaging existing research teams to collaborate internationally and contribute evidence to answer the prioritised research topics. The JPIAMR Virtual Research Institute has offered to provide a platform to achieve that by increasing coordination, improving visibility and facilitating knowledge exchange globally (https://www.jpiamr.eu/activities/jpiamr-virtual-research-institute/). A promising innovative solution for contributing generalisable evidence is 'implementation laboratories' [29] - such as for the one proposed for audit and feedback (http://www.ohri.ca/auditfeedback/). For ASPs this would involve a research team integrated into healthcare systems undertaking research projects directly relevant to the healthcare systems' priorities for ASPs. This could offer a much-needed platform for moving forward from small-scale studies developed on an *ad hoc* basis, towards co-ordinated large-scale initiatives focusing on applied research, to develop, implement and evaluate theoretically-informed ASPs in different contexts. Sufficient and sustainable resources to support further research efforts are needed to take this agenda forward. According to Chalmers et al, "research funders have primary responsibility for reduction in waste resulting from decisions about what research to do" [23], hence should be encouraged to integrate set research priorities into their organisational plans, research strategies and funding calls [23].

Our aim was to further optimise ASPs for hospital inpatients, based on experiences of research partners from HICs. Globally, the majority of prescribing

takes place in LIMICs [3]. We fully agree with proposals to advance antibiotic stewardship research in those countries [4,24] - as evident in the fact that most of our group members collaborate with research partners in LMICs. However, the health research capacity strengthening research field with a focus on implementation science is emerging, and currently evidence bases are not yet sufficiently advanced to effectively inform health research capacity strengthening research programme planning [30]. Based on our best knowledge and experiences, we recognised that implementation of ASPs varies greatly across types of healthcare systems, let alone LMICs, so inviting a limited number partners from LMICs was likely to unfairly prioritise specific research needs in their countries. We expect a similar consensus procedure to be conducted with a range of front-line clinicians and academics from LMICs with extensive experience with antibiotic prescribing in partnership with experts in implementation, intervention design and behavioural sciences from HICs and LMICs. More robust qualitative research investigating contextual influences on ASPs is needed from LMICs to inform such a consensus procedure.

We did not include patients whose role in hospital antibiotic stewardship was traditionally limited, but now is starting to increase [31]. We anticipated that a major practical challenge to include patients would be a need to overcome patient-reported doubts on their ability to understand antibiotic use-related medical information [31]. We expect that including patients would affect the completeness of the prioritised areas; hence this is needed. As recommended by Nasser et al [17], improving and refining the proposed research priorities should be continued, so we encourage assessment, revisions and updates of our consensus process at intervals of 2 years, including involvement of other stakeholders (e.g. patients). Single systematic literature reviews around each priority topic could be conducted, where numbers and types of scientific publications could serve as a proxy to quantitatively assess the impact of our research priority areas.

Conclusions

We propose 10 research priorities areas - shared by clinicians, clinical and non-clinical academics from HICs with publicly-funded health care systems - for future

research on hospital antibiotic stewardship programmes. For this we focused on a behavioural science perspective – currently underutilised in antibiotic stewardship studies [3,14,15,32]. This way we addressed a recognised important gap in knowledge [14]. We specified how optimising implementation of ASPs will depend on the use of theoretical and empirical evidence from behavioural science for knowledge synthesis; investigation of implementation failures; informing the improved design and evaluation of effectiveness, sustainability and scalability of ASPs as quality improvement initiatives.

Conflict of interest

There are no conflicts of interest to declare.

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Author contribution

MR, KG, EMD, CRR, JMG: conceived and designed the prioritisation activity; KG, EMD: acted as group facilitators; EC, JE, PGD, EMD, JJF, KG, FL, CAM, JM, RM, AMM, CRR, MR, SRVK, BS, IS, KNS, JMG: prioritised research topics; All authors: drafting the article or revising it critically for important intellectual content; All authors: final approval of the version to be submitted consensus paper.

Figure legend:

Figure 1 The stages of the research priorities setting process for antibiotic stewardship programmes in hospital settings.

Table 1 The prioritised 10 research topics (an overarching aspiration: more impactful hospital antibiotic stewardship programmes).

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Table 1 The prioritised 10 research topics (an overarching aspiration: more impactful hospital antibiotic stewardship programmes)

Research priority area	Overall ranking
Theme I. Establishing the evidence base and understanding current practice in antibiotic stewardship programmes:	
Comprehensively identifying barriers and facilitators to implementing antibiotic stewardship programmes and clinical recommendations intended to optimise antibiotic prescribing (*i.e.* good clinical practice for antibiotic use).	4
Identifying actors ('who') and actions ('what needs to be done') of antibiotic stewardship programmes and clinical teams.	6
Synthesising available evidence to support future research and planning for antibiotic stewardship programmes.	7
Specifying the activities in current antibiotic stewardship programmes with the purpose of defining a 'control group' for comparison with new initiatives.	8
Theme II: Design and evaluation of antibiotic stewardship programmes:	
Defining a balanced set of outcomes and measures to evaluate the effects of interventions focused on reducing unnecessary exposure to antibiotics.	1
Conducting robust evaluations of antibiotic stewardship programmes with built-in process evaluations and fidelity assessments.	2
Defining and designing antibiotic stewardship programmes.	5
Theme III. Research priority topics crosscutting to themes I and II:	
Establishing the evidence base for impact of antibiotic stewardship programmes on resistance.	3
Investigating the role and impact of government and policy contexts on antibiotic stewardship programmes.	9
Understanding what matters to patients in antibiotic stewardship programmes in hospitals.	10[¥]

[¥] The involvement of patients in hospital antibiotic stewardship research has been traditionally very limited, hence was ranked as no. 10. This is because patients treated with antimicrobials in hospital settings are typically more ill than patients treated in primary care, hence they may have less capacity to make their own decisions about their care.