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

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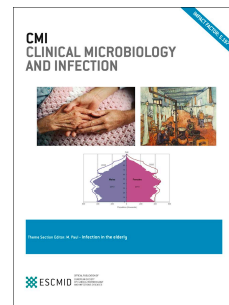
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1 **Prioritising research areas for antibiotic stewardship programmes in**
2 **hospitals: a behavioural perspective consensus paper**

3

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44

45 Abstract**46 Scope**

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

54 Methods

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

62 Question addressed and recommendations

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

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

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

87

88

89

90 **Scope**

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

99 **Context**

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

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

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

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

153 Question addressed

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

156 Methods*157 Description of the development group*

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

174 Consensus procedure

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

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

186 The stages of the priority setting process were informed by existing literature
187 [18] and are summarised in Figure 1. We used the nominal group technique (NGT) - a
188 commonly used formal consensus development method involving a highly structured
189 face-to-face group interaction. Practical benefits for which we chose the NGT
190 included: immediate dissemination of results to the group [19], giving equal voice to
191 each participant by encouraging individual input [19], reduction of personality
192 effects (*e.g.* influences of a power structure) and creating an environment conducive
193 to initiation of change [20]. In our experience research needs within the area of
194 behavioural approaches to ASPs are vast and intertwined. Also, in practice, specific
195 research questions are likely to vary across systems and specific settings [8].
196 Therefore, similar to Healy and colleagues [21], we used a modified James Lind
197 Alliance (JLA) process [22] that led to suggesting unique broad general prioritisation
198 research areas rather than specific research questions.

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

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

220 Participants were brought together through discussion and inductively
221 collated overlapping research ideas into topics. In the JLA process of priority setting –
222 a well-established framework – typically the main focus is to agree the list of the Top
223 10 priorities for future research [22]. However, to avoid artificial consensus, the
224 group was not informed about this specific number. Instead, we planned to offer the
225 group an option to decide how many research priority topics would be carried
226 forward for ranking and prepared *a priori* a strategy to reduce the number of
227 generated topics if necessary (detailed in the Supplementary Materials 1).

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

236 **Results**

237 *Consensus process*

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

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

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

260 *Recommendations*

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

277 **Implications**

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

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

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

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

336 *Conclusions*

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

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

347 **Conflict of interest**

348 There are no conflicts of interest to declare.

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361 **Author contribution**

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

367 **Figure legend:**

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

370 **Table 1** The prioritised 10 research topics (an overarching aspiration: more impactful
371 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
<i>Theme I. Establishing the evidence base and understanding current practice in antibiotic stewardship programmes:</i>	
Comprehensively identifying barriers and facilitators to implementing antibiotic stewardship programmes and clinical recommendations intended to optimise antibiotic prescribing (<i>i.e.</i> 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
<i>Theme II: Design and evaluation of antibiotic stewardship programmes:</i>	
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
<i>Theme III. Research priority topics crosscutting to themes I and II:</i>	
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.