



HAL
open science

Systematic review of factors promoting behaviour change towards antibiotic use in hospitals

Emilie Pouly, Maider Coppry, Anne-Marie Rogues, Catherine Dumartin

► **To cite this version:**

Emilie Pouly, Maider Coppry, Anne-Marie Rogues, Catherine Dumartin. Systematic review of factors promoting behaviour change towards antibiotic use in hospitals. *Clinical Microbiology and Infection*, In press, <10.1016/j.cmi.2022.01.005>. <hal-03578233>

HAL Id: hal-03578233

<https://hal.science/hal-03578233v1>

Submitted on 22 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY 4.0 - Attribution - International License

1 **TITLE PAGE**

2

3 **Category:** Systematic review - Antibiotic stewardship

4

5 **Title**

6 Systematic review of factors promoting behaviour change towards antibiotic use in hospitals

7

8 **Authors and institutional affiliations**

9 Emilie Pouly¹, Maïder Coppry^{1,2}, Anne-Marie Rogues^{1,2}, Catherine Dumartin^{2,3}

10 ¹Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, Team
11 Pharmacoepidemiology, UMR 1219, F-33000 Bordeaux, France.

12 ²CHU Bordeaux, Hygiène Hospitalière, Bordeaux, France.

13 ³CHU Bordeaux, CPias Nouvelle-Aquitaine, Bordeaux, France.

14

15 **Corresponding author**

16 Dr Catherine Dumartin

17 CPias Nouvelle-Aquitaine. Hôpital Pellegrin CHU de Bordeaux. Place Amélie Raba-Léon,

18 Bâtiment Le Tondu, 33076 Bordeaux, France

19 Tel. +33 (0)5 56 79 60 58

20 Fax. +33 (0)5 56 79 60 12

21 Email: catherine.dumartin@u-bordeaux.fr

22

23 **Length of abstract:** 299 words

24 **Length of the paper itself (excluding abstract and references):** 3,181 words

25 **ABSTRACT**

26 **Background:** Antimicrobial stewardship (AMS) programmes include actions to improve
27 antibiotic use.

28 **Objective:** To identify factors of AMS interventions associated with behaviour change
29 towards antibiotic use in hospitals, applying behavioural sciences.

30 **Data sources:** The following online databases were searched: PubMed and Scopus.

31 **Study eligibility criteria:** Studies published between January 2015 and December 2020.
32 Outcomes required were: effect of the intervention reported in terms of antibiotic
33 consumption, antibiotic costs, appropriateness of prescription, duration of therapy, proportion
34 of patients treated with antibiotics, or time to appropriate antibiotic therapy.

35 **Participants:** Healthcare professionals involved in antibiotic prescription and use in
36 hospitals, and patients receiving or susceptible to receive antibiotics.

37 **Interventions:** Studies investigating AMS interventions in hospitals.

38 **Assessment of risk of bias:** Risk of bias was determined using the “Integrated quality criteria
39 for review of multiple study designs” (ICROMS) tool.

40 **Methods of data synthesis:** Systematic review of AMS interventions, using “Behaviour
41 Change Wheel” to identify behaviour changes functions of interventions, and “Action, actor,
42 context, target, time (AACTT)” framework to describe how they are implemented.
43 Relationships between intervention functions and AACTT domains were explored to deduce
44 factors for optimal implementation.

45 **Results:** Among the 124 studies reporting 123 interventions, 64% were effective in reducing
46 antibiotic use or improving quality of antibiotic prescription. 91% of the studies had high risk
47 of bias. Main functions retrieved in effective interventions were enablement, environmental
48 restructuring, and education. The most common subcategories were audit and feedback and
49 real-time recommendation for enablement function; and material resources, human resources,

50 and new task for environmental restructuring function. Most AMS interventions focused on
51 prescription, targeted prescribers, and were implemented by pharmacists, infectious diseases
52 specialists, and microbiologists. Interventions focusing on specific clinical situation were
53 effective in 70% of cases.

54 **Conclusion:** Knowledge of factors associated with behaviour changes will help addressing
55 local barriers and enablers before implementing interventions.

56 The review protocol was registered in the International prospective register of systematic
57 reviews (PROSPERO CRD42021243939).

58 INTRODUCTION

59 The emergence and worldwide spread of antimicrobial resistance (AMR) is so alarming that
60 tackling AMR has become a high priority for the World Health Organization [1].

61 In human medicine, AMR is associated with morbidity and mortality [2] and leads to
62 prolonged hospital stay and increased health care costs [3]. One major driver of AMR is
63 inappropriate use of antibiotics through the selection pressure mechanism [4]. Thus,
64 improving antibiotic prescribing is a global emergency.

65 Hospitals are particularly affected by AMR [2]: inpatients generally present several risk
66 factors, receive invasive care, and are often exposed to antibiotics for prophylaxis or
67 treatment. Thus, improving antibiotic use in hospital context is challenging [5].

68 Antimicrobial stewardship (AMS) has been defined as “a coherent set of actions which
69 promote using antimicrobials responsibly” [6]. AMS programmes generally consist of
70 organizational policy and practice-based interventions. AMS interventions improve
71 appropriate antibiotic use and patients’ outcomes, reduce AMR and health-care-associated
72 infections, and save health-care costs [7–9]. However, variations in objectives and
73 improvement strategies among hospitals and countries have been reported [6,10].

74 Indeed, improving antibiotic use is challenging because it depends on human factors within a
75 context of a wide social network with continuous interactions between physicians, nurses,
76 pharmacists, microbiologists, and patients. Behaviour change approaches are recommended
77 to take into account psychological determinants [11], to optimise AMS interventions locally
78 in hospitals and to maximise efficient implementation worldwide [1,7,12–14].

79 For example, interventions to change healthcare professionals’ behaviours can be
80 characterized with nine functions from the “Behaviour Change Wheel” (BCW) [15]. This
81 classification has already been used [7,16] to better describe AMS activities.

82 Furthermore, detailing the context for interventions implementation helps to clarify how it
83 affects interventions effectiveness. The “Action, actor, context, target, time (AACTT)”
84 framework [17] proposes five domains to describe interventions [16,18].

85 Understanding intervention functions and context should help to identify barriers and enablers for
86 implementation of successful AMS activities. Indeed, implementation science has been defined
87 as “scientific study of methods to promote the systematic uptake of research findings and
88 other evidence-based practices into routine practice, and, hence, to improve health services”
89 [19,20].

90 Previous literature reviews investigating appropriate antibiotic use in the hospital setting
91 aimed to estimate the effectiveness and safety of interventions [7–9]. However, factors that
92 make AMS interventions effective were not often precisely described.

93 Considering that improvements in the reported outcomes regarding antibiotic use was the
94 result of a change in healthcare professionals’ behaviour, we conducted a systematic review
95 to identify the most relevant factors that promote behaviour change towards antibiotic use in
96 hospitals. We used behavioural sciences to identify the functions of AMS interventions
97 related to changes in healthcare professionals’ behaviours [15], and to describe how
98 interventions are implemented [17].

99 **METHODS**

100 **Search strategy, data sources and selection process**

101 The “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA)
102 guidelines were used to conduct this systematic review (Supplementary Table S1) [21]. The
103 review protocol was registered in the International prospective register of systematic reviews
104 (PROSPERO CRD42021243939).

105 A systematic search was conducted electronically, using PubMed and Scopus databases. The
106 search included articles published from 01/01/2015 to 12/31/2020.

107 The search strategy on PubMed combined the subject headings and free text keywords
108 “antibacterial agents” AND “drug misuses” OR “antimicrobial stewardship” OR
109 “inappropriate prescribing” OR “organizational policy” OR “health behaviour” OR “health
110 knowledge, attitudes, practice” OR “decision making” OR “behavioural science” OR
111 “attitude of health personnel” OR “guideline adherence” OR “barrier*” OR “perception”
112 AND “hospitals”.

113 The search strategy on Scopus combined the free text keywords “antibiotic*” OR
114 “antimicrobial*” OR “antibacterial agent*” AND “perception” OR “behaviour” OR
115 “attitude*” OR “guideline adherence” OR “barrier*” OR “facilitator*” OR “knowledge” OR
116 “practice*” OR “misuse” OR “*appropriate*” OR “stewardship” OR “implementation” AND
117 “health* facilit*” OR “hospital*”.

118 Three reviewers performed article screening, according to inclusion criteria. Studies included
119 in the systematic review were assessed and data were collected in duplicate by three
120 reviewers. Potentially additional studies were searched using the reference lists of included
121 articles.

122 **Study eligibility criteria**

123 The scope of the search was literature investigating AMS interventions in hospitals. Other
124 inclusion criteria were:

- 125 • Country: Studies performed in countries with national guidelines on antimicrobial
126 stewardship for public and private hospitals involving actors such as infectious
127 diseases (ID) specialists, pharmacists, and microbiologists (i.e., European Union
128 member states, South Africa, Australia, Canada, United States of America, Iceland,
129 Norway, New-Zealand, Switzerland, and the United Kingdom).

- 130 • Population: Healthcare professionals involved in the process of antibiotic prescription
131 and use in hospitals (i.e., physicians, nurses, pharmacists, microbiologists, infection
132 control professionals, AMS teams, hospital managers) and patients receiving or
133 susceptible to receive antibiotics.
- 134 • Study design: Randomised controlled trials (RCT), controlled interrupted time series
135 studies (CITS), non-controlled interrupted time series studies (NCITS), controlled
136 before-after studies (CBA), non-controlled before-after studies (NCBA), and cohort
137 studies (CS).
- 138 • Outcomes: Effect of the intervention on AMS reported in terms of antibiotic
139 consumption, antibiotic costs, appropriateness of prescription, duration of therapy,
140 proportion of patients treated with antibiotics, and time to appropriate antibiotic
141 therapy.

142 We excluded studies not clearly describing AMS interventions, studies exploring AMS
143 interventions in nursing homes, and studies involving healthcare professionals not working in
144 hospitals. We also excluded qualitative study design, systematic reviews of interventions
145 targeting antibiotic use in hospitals, and case studies.

146 **Data collection**

147 By using a collection form, we performed data extraction and quality assessment of included
148 studies in duplicate.

149 **Assessment of risk of bias**

150 The risk of bias (ROB) was determined using the “Integrated quality criteria for review of
151 multiple study designs” (ICROMS) tool [22]. Disagreements were resolved through
152 discussion.

153 **Methods of data analysis and synthesis**

154 From AMS activities reported in included articles, we extracted the different factors
155 described and we classified them using the BCW framework [15]. BCW classification
156 identifies nine intervention functions: coercion, education, enablement, environmental
157 restructuring, incentivisation, modelling, persuasion, restriction, and training (Supplementary
158 Table S2). A given intervention may involve more than one behaviour change function. To
159 better describe intervention functions, we made subcategories for enablement function (alert,
160 algorithm, audit and feedback, decision aid tool, feedback on prescribing practices, real-time
161 recommendation), and for environmental restructuring function (human resources, material
162 resources, new diagnostic tool, new task).

163 We applied an adapted AACTT framework [17] to clearly describe interventions in AMS
164 context. We only described the main AMS action for which behaviour change was sought,
165 using the following modified AACTT definitions (Supplementary Table S3):

- 166 • Action: discrete observable behaviour to be changed (antibiotic administration,
167 diagnosis, initial prescription, review of prescription, prescription at discharge,
168 surgical prophylaxis prescription, and therapeutic drug monitoring);
- 169 • Actor: individual or group of individuals who conduct the intervention to change the
170 behaviour;
- 171 • Context: the physical, emotional, or social setting in which the actor performs the
172 intervention (focus on wards or clinical situation or specific antibiotics, AMS
173 programme or team already in place);
- 174 • Target: the individual or group of individuals who receive the intervention to change
175 their behaviour to perform the action;
- 176 • Time: the time period and duration that the actor performs the intervention.

177 We determined categories for intervention effectiveness based on study outcomes defined
178 above. Interventions with significant outcomes were categorised as “effective interventions”,
179 and interventions with non-significant outcomes as “not effective interventions”. When
180 studies had both significant and non-significant outcomes, priority was given to primary
181 outcome; if primary outcome was not clearly defined or was not an outcome of interest,
182 interventions were classified as “inconclusive”.
183 In effective interventions, we explored relationships between AACTT domains and
184 intervention functions to identify main factors retrieved.

185 **RESULTS**

186 The electronic search retrieved 830 publications. We identified 63 potential additional
187 publications from reference list of included articles, resulting in a total of 875 publications
188 after removal of duplicates. Title and abstract screening resulted in 205 full texts to assess.
189 Finally, 124 studies met inclusion criteria for further analysis, reporting 123 AMS
190 interventions (Figure 1 and Supplementary material Table S4).

191 **Study characteristics and risk of bias assessment**

192 Of the 124 studies, there were eight RCT, five CITS, 31 NCITS, three CBA, 76 NCBA, and
193 one CS (Table 1). Most studies were conducted in North America (68 in United States of
194 America and 11 in Canada). A total of 24 studies were conducted in the European Union,
195 eight in Australia, and six in the United Kingdom.

196 According to ICROMS risk of bias assessment tool, 11 studies were judged as low ROB: two
197 RCT, one CITS, one CBA, six NCBA, and one CS (Table 1).

198 **Intervention functions of AMS interventions promoting behaviour change in hospitals**

199 Among the 123 interventions, 328 intervention functions were identified (Figures 2a and 2b;
200 median number of intervention functions = 2; min = 1; max = 5).

201 Of the nine intervention functions described in BCW, only coercion was not reported in any
202 intervention. Enablement, environmental restructuring, and education were the most
203 frequently intervention functions identified. Incentivisation, modelling and training were the
204 less frequently identified. Among enablement function, the most common subcategory was
205 audit and feedback. Among environmental restructuring function, the most common
206 subcategories were material resources and human resources.

207 **Conditions of AMS interventions implementation**

208 When modified AACTT framework was applied, all domains were described in 80% of
209 interventions (99/123). Actor and time were among the least often described (Table 2).

210 The most common action in AMS interventions was prescribing.

211 The actor was clearly specified in 88% of interventions. The median number of actors
212 categories involved per intervention was two (min = 1; max = 4). In 23% of interventions,
213 actors were included within an AMS team, defined as a group of healthcare professionals
214 working together to perform the main activity of the intervention.

215 Pharmacists were involved in 75 interventions, ID specialists in 65 interventions, and
216 microbiologists in 26 interventions. Nurses were involved in six interventions.

217 Half of interventions (50%) focused on specific clinical situations: bloodstream infections (20
218 interventions), respiratory tract infections (13 interventions), urinary tract infections (seven
219 interventions), and antibiotic allergies (six interventions).

220 One third of interventions (32%) focused on specific wards: emergency department (nine
221 interventions), surgical units (eight interventions), and intensive care units (seven
222 interventions).

223 The most common target was the prescriber i.e., medical physicians, medical and surgical
224 residents, anaesthesia specialists, and surgeons. Two interventions also targeted patients in
225 the specific context of antibiotic allergy, where patients received information (i.e., written
226 recommendations regarding the revised antibiotic allergy labels and antibiotics that could be
227 safely administered).

228 The time period and duration of the main intervention action was clearly specified in 90% of
229 interventions: interventions were mainly performed within 24 hours.

230 **Functions and conditions of AMS interventions associated with an improvement in** 231 **antibiotic use in hospitals**

232 A total of 79 interventions (i.e., 64%) were categorised as “effective”, 33 as “inconclusive”,
233 and 11 as “not effective” (Table 1). We identified 211 intervention functions among the 79
234 effective interventions (median number of intervention functions = 2; min = 1; max = 5).

235 The most effective intervention functions (Figure 2a) were restriction (72% of interventions
236 using restriction were effective); environmental restructuring (65%); education (65%); and
237 enablement (63%). Among environmental restructuring function (Figure 2b), the most
238 effective subcategories were new task (81%) and material resources (70%). Among
239 enablement function, the most effective subcategories were real-time recommendation (77%),
240 algorithm (75%), and alert (70%).

241 The three most common intervention functions identified in effective interventions were
242 enablement, environmental restructuring, and education, with differences in the subcategories
243 for enablement and environmental restructuring functions.

244 According to action types

245 In effective interventions aimed at improving initial prescription (35/47), main subcategories
246 identified among enablement function were audit and feedback and real-time

247 recommendation. Among environmental restructuring function, main subcategory was
248 material resources.

249 According to actor category

250 In effective interventions involving one category of actor (24/40), main subcategory of
251 enablement was audit and feedback. Among environmental restructuring, main subcategories
252 were material resources and human resources.

253 In effective interventions involving more than one category of actor (28/40), main
254 subcategories of enablement were audit and feedback and real-time recommendation. Among
255 environmental restructuring, main subcategories were material resources and new task.

256 In effective interventions where actors were part of an AMS team (17/28), education was not
257 among the main intervention functions. Main subcategories of enablement were real-time
258 recommendation and audit and feedback. Among environmental restructuring, main
259 subcategories were human resources and new task.

260 According to the context

261 In effective interventions focusing on specific clinical situation (43/61), main subcategories
262 of enablement were real-time recommendation and audit and feedback. Among
263 environmental restructuring, main subcategories were material resources and new task. All
264 seven interventions focusing on bloodstream infections and combining real-time
265 recommendation and new diagnostic tool performed within 24 hours were effective.

266 In effective interventions focusing on specific antibiotics (33/52), interestingly, we identified
267 restriction in addition to the three main intervention functions (e.g., pharmacist prospective
268 review of all respiratory fluoroquinolone orders for consistency with the approved restriction
269 criteria; pre-authorisation by a pharmacist or an ID specialist).

270

271

272 According to the time

273 In effective interventions performed within 24 hours (54/85), main subcategories identified
274 among enablement were audit and feedback and real-time recommendation; it was audit and
275 feedback in effective interventions performed between 24 hours and 7 days (10/14).

276 As targets other than antibiotic prescribers were rare, we did not describe distribution of
277 intervention functions for this domain.

278 **DISCUSSION AND CONCLUSION**

279 We conducted this systematic review in order to identify the conditions of implementation of
280 AMS interventions and BCW intervention functions associated with improvement in
281 antibiotic use. We described multimodal interventions involving multiple behaviours and
282 most of them were assessed as effective in reducing antibiotic use or improving quality of
283 antibiotic prescription. Potential publication bias and inclusion of studies with high risk of
284 bias must be considered to interpret this finding.

285 When we explored functions used in effective interventions according to the conditions of
286 implementation (i.e., regarding AACTT domains), we retrieved three main functions:
287 enablement, environmental restructuring, and education. Surprisingly, in interventions
288 involving AMS team, education was not among the most frequent functions. This may result
289 from previous educational activities performed by AMS team before intervention
290 implementation [23]. As expected, restriction function was retrieved across the main
291 functions used in interventions focusing on specific antibiotics. This is consistent with
292 European Union guidelines [12] that recommend performing “policy for pre-authorisation
293 [...] of selected antimicrobial prescriptions” and AMS practices in United States hospitals
294 [23].

295 Enablement was one of the most common intervention functions in effective interventions.
296 This is consistent with findings of Davey *et al* who found that involving enablement and
297 restriction functions increased intervention effect [7]. Environmental restructuring was the
298 second most common intervention function identified. In their systematic review, Crayton *et*
299 *al* reported that “interventions involving enablement, environmental restructuring and
300 delivery of audit and feedback strategies were likely to enhance AMS” in nursing homes
301 [16]. This suggests that similar intervention components might be promising in the hospital
302 setting.

303 The most common subcategories of enablement in effective interventions were audit and
304 feedback and real-time recommendation. These findings show the relevance of implementing
305 audit and feedback, as recommended in European AMS guidelines [12], and in line with
306 another systematic review [24].

307 The detailed description of AACTT domains revealed the need for improving the
308 multidisciplinary of AMS activities. Indeed, AMS is a multidisciplinary approach [6],
309 recognized as a strong international recommendation [12]. However, an AMS team was
310 mentioned in only 23% of interventions. This finding is consistent with a previous review
311 [18] and calls for efforts to increase the availability of qualified professionals to conduct
312 AMS activities. Furthermore, targets of the studied interventions always included prescribers,
313 for the action of prescribing antibiotics. Yet, the prescribing process involves various
314 healthcare professionals in several steps. Surprisingly, in only 5% of interventions, nurses
315 were targeted although many publications showed the interest of their involvement in AMS
316 [25,26]. This description reveals room for improvement in action and target diversity in AMS
317 interventions.

318 When considering specific conditions of implementation, as defined by AACTT domains,
319 some subcategories were most commonly involved in effective interventions.

320 In effective interventions aimed at improving initial prescription, audit and feedback and real-
321 time recommendation were frequently performed. Interventions using real-time
322 recommendation seemed to be more often effective compared to audit and feedback
323 performed within 24 hours. In fact, modifying a prescription already issued or after drug
324 dispensation or administration may appear more complex and less acceptable for the
325 prescriber. Thus, the difference in effectiveness for audit and feedback and real-time
326 recommendation could be explained by prescribers' perceptions. This finding suggests the
327 importance of choosing intervention function according to available resources and ability to
328 act at the right time.

329 When interventions involved one category of actors, we retrieved most frequently human
330 resources subcategory. This suggests that implementing an AMS intervention involving one
331 single actor was made possible by recruiting healthcare professionals or by identifying
332 dedicated time for professionals already working in the institution. This finding is in line with
333 European AMS guidelines that require that healthcare facilities provide the necessary funding
334 and resources for AMS programmes [12].

335 Regarding the context, half of interventions focused on a specific clinical situation and
336 seemed to be associated with interventions effectiveness (70% of effectiveness). In
337 interventions focusing on a specific clinical situation, prescriber's commitment may be
338 enhanced because clinical outcomes are measured and/or because serious situations are
339 addressed. Among bloodstream infections, all interventions combining real-time
340 recommendation and new diagnostic tool functions performed within 24 hours were effective.

341 **Strengths and limitations**

342 To our knowledge this is the first study that used two complementary behavioural sciences
343 frameworks [15,17] to explore implementation of AMS strategies in hospitals. In addition, to
344 improve description of AMS interventions, a strength of this systematic review is the

345 specification of subcategories for enablement and environmental restructuring functions.
346 Finally, despite no clear association between BCW functions and effectiveness, the large
347 number of references included allowed us to clearly describe interventions and, thus, to
348 identify criteria of interest to achieve optimal conditions for implementation of AMS
349 interventions in hospitals.

350 This study has several limitations. First, we limited our search to PubMed and Scopus. Other
351 databases could have brought additional references. Second, identification of BCW
352 intervention functions and AACTT domains was sometimes challenging as authors
353 description could give way to different interpretations. Nevertheless, we discussed on
354 disagreements to harmonize classifications. Third, 91% of studies had high ROB. This is
355 consistent with findings from previous work and calls for significant improvements in the
356 methods of AMS studies, building on professional recommendations and considering
357 integration of implementation sciences aspects [27–29]. Fourth, when assessing interventions
358 effectiveness, we focused on outcomes regarding antibiotic consumption and appropriateness;
359 we did not consider other outcomes such as clinical results. Last, we cannot rule out that
360 other factors played a role in the associations retrieved between AACTT domains and
361 intervention functions.

362 To conclude, this review highlighted relevant factors that should promote behaviour change
363 towards antibiotic use in hospitals. Interventions including enablement, environmental
364 restructuring, and education are likely to optimize antibiotic use. Taking into account the
365 context, focusing on some subcategories of enablement and environmental restructuring
366 could improve interventions effectiveness, such as performing real-time recommendation in
367 interventions aimed at improving initial prescription. Therefore, assessment of the local
368 situation before implementation of AMS activities should help to identify barriers and
369 enablers and then, to check whether all conditions are met to effectively put in place the

370 required intervention. Besides this state of play of the local situation, assessing healthcare
371 professionals' perceptions is recommended to adapt interventions and increase their
372 acceptance [19,30,31].

373 **Transparency declaration**

374 The authors declare that they have no conflicts of interest.

375 There was no specific funding for this systematic review.

376 **Authors' contributions**

377 All authors have seen and approved the manuscript, contributed significantly to the work. All
378 authors contributed equally to the study design, paper review, and data collection. E.P.
379 performed the literature search, citations screening on title and abstract, full text screening,
380 data collection, data analysis, data interpretation, figures and tables, wrote the first draft of
381 the paper and finalised the writing. C.D. and M.C. conceived the project, contributed to
382 abstract and full text screening and to data collection, reviewed all the pertinent data to check
383 their validity and provided multiple drafts of the paper. A-M. R. conceived the project and
384 provided multiple drafts of the paper.

385

386 REFERENCES

- 387 1. World Health Organization. Global action plan on antimicrobial resistance. 2015.
388 Available at: <https://www.who.int/publications/i/item/9789241509763>. Accessed 30
389 September 2021.
- 390 2. Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al.
391 Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-
392 resistant bacteria in the EU and the European Economic Area in 2015: a population-level
393 modelling analysis. *Lancet Infect Dis* 2019;19(1):56–66.
- 394 3. Naylor NR, Atun R, Zhu N, Kulasabanathan K, Silva S, Chatterjee A, et al. Estimating
395 the burden of antimicrobial resistance: a systematic literature review. *Antimicrob Resist*
396 *Infect Control* 2018;7(1):58.
- 397 4. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and
398 meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC*
399 *Infect Dis* 2014;14(1):13.
- 400 5. Goff DA, Kullar R, Bauer KA, File TM Jr. Eight habits of highly effective antimicrobial
401 stewardship programs to meet the Joint Commission Standards for Hospitals. *Clin Infect*
402 *Dis* 2017;64(8):1134-1139.
- 403 6. Dyar OJ, Huttner B, Schouten J, Pulcini C. What is antimicrobial stewardship? *Clin*
404 *Microbiol Infect* 2017;23(11):793–8.
- 405 7. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to
406 improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst*
407 *Rev* 2017;2:CD003543.

- 408 8. Nathwani D, Varghese D, Stephens J, Ansari W, Martin S, Charbonneau C. Value of
409 hospital antimicrobial stewardship programs [ASPs]: a systematic review. *Antimicrob*
410 *Resist Infect Control* 2019;8(1):1–13.
- 411 9. Schuts EC, Hulscher MEJL, Mouton JW, Verduin CM, Stuart JWTC, Overdiek HWPM,
412 et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic
413 review and meta-analysis. *Lancet Infect Dis* 2016;16(7):847–56.
- 414 10. Kallen MC, Binda F, ten Oever J, Tebano G, Pulcini C, Murri R, et al. Comparison of
415 antimicrobial stewardship programmes in acute-care hospitals in four European
416 countries: a cross-sectional survey. *Int J Antimicrob Agents* 2019;54(3):338–45.
- 417 11. Charani E, Castro-Sanchez E, Sevdalis N, Kyratsis Y, Drumright L, Shah N, et al.
418 Understanding the determinants of antimicrobial prescribing within hospitals: the role of
419 “Prescribing Etiquette”. *Clin Infect Dis* 2013;57(2):188–96.
- 420 12. European Commission. European Union guidelines for the prudent use of antimicrobials
421 in human health. 2017. Available at: [https://ec.europa.eu/health/antimicrobial-](https://ec.europa.eu/health/antimicrobial-resistance/eu-action-on-antimicrobial-resistance_en)
422 [resistance/eu-action-on-antimicrobial-resistance_en](https://ec.europa.eu/health/antimicrobial-resistance/eu-action-on-antimicrobial-resistance_en). Accessed 30 September 2021.
- 423 13. Comité Interministériel pour la Santé. Interministerial roadmap for controlling
424 antimicrobial resistance. 2016. Available at: [https://solidarites-](https://solidarites-sante.gouv.fr/IMG/pdf/interministerial_amr_roadmap_en.docx.pdf)
425 [sante.gouv.fr/IMG/pdf/interministerial_amr_roadmap_en.docx.pdf](https://solidarites-sante.gouv.fr/IMG/pdf/interministerial_amr_roadmap_en.docx.pdf). Accessed 30
426 September 2021.
- 427 14. Inserm. Priority research programme on antibiotic resistance. 2021. Available at:
428 [https://ppr-antibioresistance.inserm.fr/en/antibiotic-resistance-priority-research-](https://ppr-antibioresistance.inserm.fr/en/antibiotic-resistance-priority-research-programme/objectives-of-the-antibiotic-resistance-programme/)
429 [programme/objectives-of-the-antibiotic-resistance-programme/](https://ppr-antibioresistance.inserm.fr/en/antibiotic-resistance-priority-research-programme/objectives-of-the-antibiotic-resistance-programme/). Accessed 30 September
430 2021.

- 431 15. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for
432 characterising and designing behaviour change interventions. *Implement Sci*
433 2011;6(1):42.
- 434 16. Crayton E, Richardson M, Fuller C, Smith C, Liu S, Forbes G, et al. Interventions to
435 improve appropriate antibiotic prescribing in long-term care facilities: a systematic
436 review. *BMC Geriatr* 2020;20(1):237.
- 437 17. Pesseau J, McCleary N, Lorencatto F, Patey AM, Grimshaw JM, Francis JJ. Action,
438 actor, context, target, time (AACTT): a framework for specifying behaviour. *Implement*
439 *Sci* 2019;14(1):102.
- 440 18. Duncan EM, Charani E, Clarkson JE, Francis JJ, Gillies K, Grimshaw JM, et al. A
441 behavioural approach to specifying interventions: what insights can be gained for the
442 reporting and implementation of interventions to reduce antibiotic use in hospitals? *J*
443 *Antimicrob Chemother* 2020;75(5):1338–46.
- 444 19. Bauer MS, Damschroder L, Hagedorn H, Smith J, Kilbourne AM. An introduction to
445 implementation science for the non-specialist. *BMC Psychol* 2015;3:32.
- 446 20. Eccles MP, Mittman BS. Welcome to implementation science. *Implement Sci* 2006; 1(1).
- 447 21. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items
448 for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*
449 2009;6(7):e1000097.
- 450 22. Zingg W, Castro-Sanchez E, Secci FV, Edwards R, Drumright LN, Sevdalis N, et al.
451 Innovative tools for quality assessment: integrated quality criteria for review of multiple
452 study designs (ICROMS). *Public Health* 2016;133:19–37.

- 453 23. Nhan D, Lentz EJM, Steinberg M, Bell CM, Morris AM. Structure of Antimicrobial
454 Stewardship Programs in Leading US Hospitals: Findings of a Nationwide Survey. *Open*
455 *Forum Infect Dis* 2019;6(4):ofz104.
- 456 24. Araujo da Silva AR, Albernaz de Almeida Dias DC, Marques AF, Biscaia di Biase C,
457 Murni IK, Dramowski A, et al. Role of antimicrobial stewardship programmes in
458 children: a systematic review. *J Hosp Infect* 2018;99(2):117–23.
- 459 25. Monsees E, Popejoy L, Jackson MA, Lee B, Goldman J. Integrating staff nurses in
460 antibiotic stewardship: opportunities and barriers. *Am J Infect Control* 2018;46(7):737–
461 42.
- 462 26. Olans RN, Olans RD, DeMaria A Jr. The critical role of the staff nurse in antimicrobial
463 stewardship – unrecognized, but already there. *Clin Infect Dis* 2016;62(1):84-9.
- 464 27. Schweitzer VA, van Heijl I, van Werkhoven CH, Islam J, Hendriks-Spoor KD, Bielicki J,
465 et al; Consensus on Antimicrobial Stewardship Evaluations (CASE) study group. The
466 quality of studies evaluating antimicrobial stewardship interventions: a systematic
467 review. *Clin Microbiol Infect* 2019;25(5):555-561.
- 468 28. Schweitzer VA, van Werkhoven CH, Rodríguez Baño J, Bielicki J, Harbarth S, Hulscher
469 M, et al; Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) Working
470 Group on Design of Antimicrobial Stewardship Evaluations. Optimizing design of
471 research to evaluate antibiotic stewardship interventions: consensus recommendations of
472 a multinational working group. *Clin Microbiol Infect* 2020;26(1):41-50.
- 473 29. Ploy MC, Andremont A, Valtier B, Le Jeune C; participants of Giens XXXV Round
474 Table 'Translational research'. Antibiotic resistance: Tools for effective translational
475 research. *Therapie* 2020;75(1):7-12.

- 476 30. Perozziello A, Lescure FX, Truel A, Routelous C, Vaillant L, Yazdanpanah Y, et al.
477 Prescribers' experience and opinions on antimicrobial stewardship programmes in
478 hospitals: a French nationwide survey. *J Antimicrob Chemother* 2019;74(8):2451–8.
- 479 31. Warreman EB, Lambregts MMC, Wouters RHP, Visser LG, Staats H, van Dijk E, et al.
480 Determinants of in-hospital antibiotic prescription behaviour: a systematic review and
481 formation of a comprehensive framework. *Clin Microbiol Infect* 2019;25(5):538–45.

Table 1 Studies characteristics and interventions effectiveness

First author	Year	Country	Study design	Study period	Intervention effectiveness	ROB^a
Anderson	2019	USA ^b	CBA ^c	2013-2015	Effective	High
Bai	2015	Canada	CS ^d	2007-2010	Effective	Low
Blumenthal	2015	USA	NCBA ^e	2011-2014	Effective	High
Boel	2016	Denmark	CITS ^f	2008-2014	Effective	High
Bolten	2019	USA	NCBA	2015-2016	Effective	High
Bond	2017	Australia	NCBA	2013-2014	Effective	High
Bond (b)	2017	Australia	NCITS ^g	2010-2014	Effective	High
Bonsignore	2018	Germany	NCBA	2015-2016	Effective	High
Bookstaver	2017	USA	NCBA	2010-2015	Effective	High
Box	2015	USA	NCBA	2011-2014	Effective	High
Brink	2016	South Africa	NCITS	2009-2014	Effective	High
Brink	2017	South Africa	NCBA	2013-2015	Effective	High
Burston	2017	Australia	CBA	2015	Effective	High
Campbell	2017	Canada	NCITS	2009-2014	Effective	High
Chrysou	2018	Greece	NCBA	2015-2016	Effective	High
Collins	2016	USA	NCBA	2014	Effective	High
Du Plessis	2019	New Zealand	NCBA	2015	Effective	High
Eby	2018	USA	NCBA	2012-2015	Effective	Low
Flett	2018	USA	NCITS	2014-2016	Effective	High
Frymoyer	2020	USA	NCITS	2015-2019	Effective	High
Giacobbe	2017	Italy	NCBA	2014-2016	Effective	High
Gibbons	2017	USA	NCITS	2011-2012	Effective	High
Gordon	2018	USA	NCBA	2012-2015	Effective	High

Haran	2020	USA	NCBA	2017	Effective	High
Hersh	2018	USA	NCITS	2013-2015	Effective	High
Hincker	2017	USA	NCBA	2014-2015	Effective	High
Hurst	2016	USA	NCITS	2010-2014	Effective	High
Irfan	2015	Canada	CITS	2012-2013	Effective	High
James	2019	USA	NCBA	2016-2017	Effective	High
Johnson	2016	USA	NCBA	2012-2013	Effective	High
Kandel	2016	Canada	NCBA	2010-2013	Effective	High
Kashtan	2020	USA	NCBA	2017-2019	Effective	High
Kirk	2019	USA	NCITS	2012-2018	Effective	High
Lambl	2017	USA	NCBA	2013-2016	Effective	High
Langford	2016	Canada	NCITS	2008-2015	Effective	High
Langford	2019	Canada	NCITS	2012-2016	Effective	High
Leis	2017	Canada	NCBA	2015-2016	Effective	High
Lesprit	2015	France	RCT ^h	2010-2011	Effective	High
Li	2016	USA	NCBA	2010-2014	Effective	High
Libertin	2017	USA	NCBA	2013-2015	Effective	High
Lockwood	2016	USA	NCBA	2011-2014	Effective	High
Lowe	2017	Canada	NCBA	2014-2016	Effective	High
MacVane	2016	USA	NCBA	2010-2014	Effective	Low
Martin	2015	Canada	NCBA	2011-2012	Effective	High
McLellan	2016	UK ⁱ	RCT	2013	Effective	High
Mediwala	2019	USA	NCBA	2013-2017	Effective	High
Messacar	2017	USA	NCBA	2010-2015	Effective	High
Messina	2015	South Africa	NCBA	2013-2014	Effective	High
Molina	2017	Spain	NCITS	2009-2015	Effective	High
Nguyen	2015	USA	NCBA	2012-2014	Effective	High

Papadimitriou-Olivgeris	2020	Switzerland	NCBA	2014-2018	Effective	High
Patton	2018	UK	NCITS	2006-2010	Effective	High
Pettit	2018	USA	NCBA	2014-2017	Effective	High
Phillips	2018	Australia	NCBA	2010-2014	Effective	High
Picart	2016	France	NCBA	2012-2014	Effective	High
Polen	2018	USA	NCBA	2016-2017	Effective	High
Popovski	2015	Canada	NCBA	2010-2011	Effective	High
Porter	2019	USA	NCBA	2014-2017	Effective	High
Rawlins	2018	Australia	NCBA	2015-2016	Effective	High
Rosa	2018	USA	NCITS	2014-2015	Effective	High
Scholze	2015	Germany	NCBA	2010-2013	Effective	High
Schröder	2020	Germany	NCBA	2008-2017	Effective	High
Shea	2017	USA	NCBA	2013-2014	Effective	High
Spruiell	2017	USA	NCBA	2009-2014	Effective	High
Stenehjem	2018	USA	RCT	2013-2015	Effective	High
Stultz	2019	USA	NCBA	2008-2017	Effective	High
Swearingen	2016	USA	NCBA	2012-2013	Effective	High
Tamma	2017	USA	NCITS	2013-2014	Effective	High
Tedeschi	2017	Italy	NCBA	2011-2014	Effective	High
Tischendorf	2020	USA	NCITS	2014-2018	Effective	High
Townsend	2016	USA	NCBA	2010-2014	Effective	High
Trubiano	2017	Australia	NCBA	2015-2016	Effective	Low
Turner	2017	USA	NCITS	2010-2015	Effective	High
Walsh	2018	USA	NCBA	2014-2015	Effective	High
Wenzler	2017	USA	NCBA	2015-2016	Effective	Low
Wilke	2015	Germany	NCBA	2014	Effective	High
Willis	2017	USA	NCITS	2009-2015	Effective	High

Wilson	2019	USA	NCBA	2015-2016	Effective	High
Wolfe	2019	USA	NCBA	2016-2017	Effective	High
Antonioli	2018	Italy	NCBA	2014-2015	Inconclusive	High
Asencio Egea	2018	Spain	NCBA	2016-2017	Inconclusive	High
Beaulac	2016	USA	NCITS	2010-2014	Inconclusive	High
Bouza	2020	Spain	NCBA	2015-2017	Inconclusive	High
Charani	2017	UK	NCITS	2008-2014	Inconclusive	High
Cona	2020	Italy	NCBA	2016-2018	Inconclusive	High
Cross	2019	UK	NCBA	2017	Inconclusive	High
Day	2015	USA	NCBA	2008-2012	Inconclusive	High
Donà	2019	Italy	NCBA	2016-2017	Inconclusive	High
Dustin Waters	2015	USA	NCBA	2006-2012	Inconclusive	High
Eljaaly	2018	USA	NCBA	2012-2013	Inconclusive	Low
García-López	2017	Spain	NCBA	2010-2013	Inconclusive	High
García-Martínez	2016	Spain	NCBA	2011-2014	Inconclusive	High
Graber	2015	USA	NCBA	2012-2013	Inconclusive	High
Griebel	2018	USA	NCBA	2013-2017	Inconclusive	Low
Hartley	2016	USA	NCBA	2011-2013	Inconclusive	High
Hecker	2020	USA	NCBA	2013-2015	Inconclusive	High
Høgli	2016	Norway	NCITS	2014-2015	Inconclusive	High
Jenkins	2015	USA	NCITS	2005-2014	Inconclusive	High
Jenkins	2018	USA	NCITS	2014-2016	Inconclusive	High
Kreitmeyr	2017	Germany	NCBA	2014-2015	Inconclusive	High
MacBrayne	2020	USA	NCITS	2010-2018	Inconclusive	High
May	2015	USA	RCT	2011-2014	Inconclusive	Low
Morrill	2016	USA	NCITS	2010-2013	Inconclusive	High
O'Callaghan	2019	Australia	NCBA	2017-2018	Inconclusive	High

Phillips	2015	Australia	NCBA	Not specified	Inconclusive	High
Sarma	2015	UK	NCITS	2007-2012	Inconclusive	High
Taggart	2015	Canada	CITS	2012-2014	Inconclusive	Low
Tavares	2018	Portugal	CITS	2012-2016	Inconclusive	High
Trautner	2015	USA	CBA	2010-2013	Inconclusive	Low
Velasco-Arnaiz	2020	Spain	NCITS	2015-2018	Inconclusive	High
Wathne	2018	Norway	RCT	2014	Inconclusive	High
Wattier	2017	USA	NCITS	2011-2016	Inconclusive	High
Zhang	2017	USA	NCBA	2014-2015	Inconclusive	High
Bouchand	2017	France	NCBA	2012-2014	Not effective	High
Branche	2015	USA	RCT	2013-2014	Not effective	High
Brendish	2017	UK	RCT	2015-2016	Not effective	High
Klatte	2018	USA	CITS	2013-2016	Not effective	High
Nzegwu	2017	USA	NCITS	2011-2016	Not effective	High
O'Sullivan	2019	USA	NCITS	2013-2017	Not effective	High
Pitiriga	2018	Greece	NCBA	2014-2017	Not effective	High
Saarela	2020	Finland	RCT	2014-2015	Not effective	Low
Smoke	2019	USA	NCITS	2016-2017	Not effective	High
Thom	2019	USA	NCBA	2014-2015	Not effective	High
Yogo	2017	USA	NCBA	2012-2015	Not effective	High

^aROB = risk of bias; ^bUSA = United States of America; ^cCBA = controlled before-after study; ^dCS = cohort study; ^eNCBA = non-controlled before-after study; ^fCITS = controlled interrupted time series study; ^gNCITS = non-controlled interrupted time series study; ^hRCT = randomised controlled trial; ⁱUK = United Kingdom

Table 2 Action, Actor, Context, Target and Time (ACCTT) domains identified in the 123 interventions, distribution of study design and risk of bias

AACTT ^a domain		Study design	ROB ^b	Effective interventions (n)	Total interventions (n)
Action	Initial and review of prescription	3 RCT 3 CITS; 14 NCITS 28 NCBA	45 high ROB	29	48
	Initial prescription	5 RCT ^c 1 CITS ^d ; 11 NCITS ^e 2 CBA ^f ; 27 NCBA ^g 1 CS ^h	41 high ROB	35	47
	Review of prescription	1 NCITS 10 NCBA	10 high ROB	5	11
	Surgical prophylaxis prescription	1 NCITS 4 NCBA	5 high ROB	3	5
	Diagnosis and initial prescription	1 NCITS 1 CBA; 2 NCBA	3 high ROB	2	4
	Prescription at discharge	1 NCITS 2 NCBA	3 high ROB	1	3
	Initial and surgical prophylaxis prescription	1 CITS; 1 NCITS	2 high ROB	2	2
	Therapeutic drug monitoring and initial prescription	2 NCBA	2 high ROB	1	2
Antibiotic administration	1 NCBA	1 high ROB	1	1	
Actor	One category of actor	4 RCT 2 CITS; 5 NCITS 2 CBA; 26 NCBA 1 CS	38 high ROB	24	40
	More than one category of actor (excluding AMS ⁱ team)	3 RCT 2 CITS; 11 NCITS 24 NCBA	35 high ROB	28	40
	AMS team	1 CITS; 9 NCITS 18 NCBA	26 high ROB	17	28
	Not specified	1 RCT 5 NCITS 1 CBA; 8 NCBA	13 high ROB	10	15
Context	Specific clinical situation	4 RCT 2 CITS; 9 NCITS 2 CBA; 43 NCBA 1 CS	54 high ROB	43	61
	AMS programme or team already in place	1 RCT 2 CITS; 20 NCITS 1 CBA; 29 NCBA	48 high ROB	36	53
	Specific antibiotics	1 RCT 3 CITS; 16 NCITS 1 CBA; 31 NCBA	33 high ROB	33	52
	Specific wards	6 RCT 3 CITS; 11 NCITS 1 CBA; 18 NCBA	35 high ROB	19	39

Target	Prescribers	8 RCT 5 CITS; 29 NCITS 2 CBA; 69 NCBA 1 CS	105 high ROB	73	114
	Prescribers and nurses	1 NCITS 1 CBA; 2 NCBA	3 high ROB	3	4
	Prescribers, nurses, microbiologists, and pharmacists	2 NCBA	2 high ROB	0	2
	Prescribers and patients	2 NCBA	1 high ROB	2	2
	Not specified	1 NCBA	1 high ROB	1	1
Time	Within 24 hours	6 RCT 1 CITS; 19 NCITS 2 CBA; 57 NCBA	76 high ROB	54	85
	Between 24 hours and 7 days	1 RCT 2 CITS; 4 NCITS 7 NCBA	14 high ROB	10	14
	Other (after 7 days or punctual sessions)	1 RCT 2 CITS; 2 NCITS 1 CBA; 6 NCBA	11 high ROB	6	12
	Not specified	5 NCITS 6 NCBA 1 CS	11 high ROB	9	12

^aAACTT = action, actor, context, target, time; ^bROB = risk of bias; ^cRCT = randomised controlled trial; ^dCITS = controlled interrupted time series study; ^eNCITS = non-controlled interrupted time series study; ^fCBA = controlled before-after study; ^gNCBA = non-controlled before-after study; ^hCS = cohort study; ⁱAMS = antimicrobial stewardship

Figure 1 Study flow diagram (PRISMA)

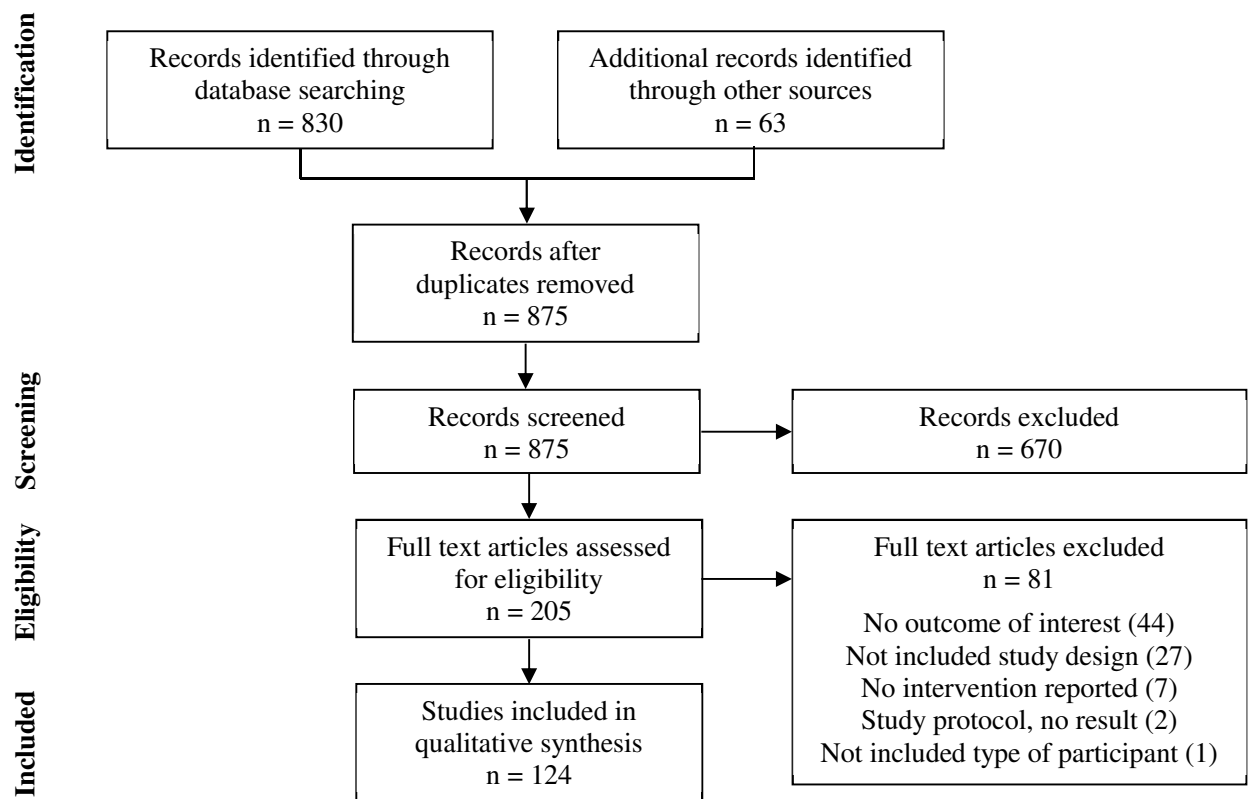
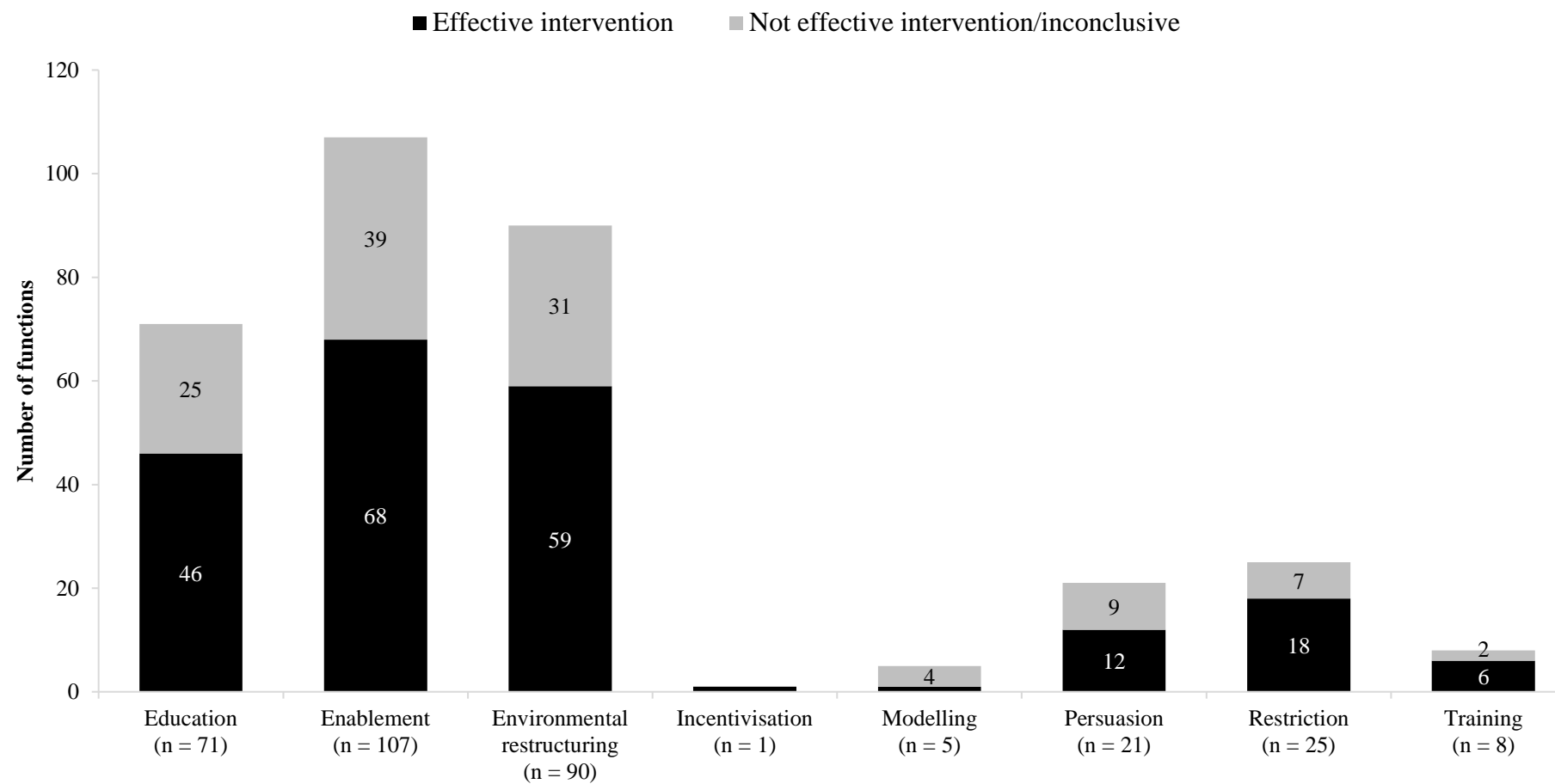
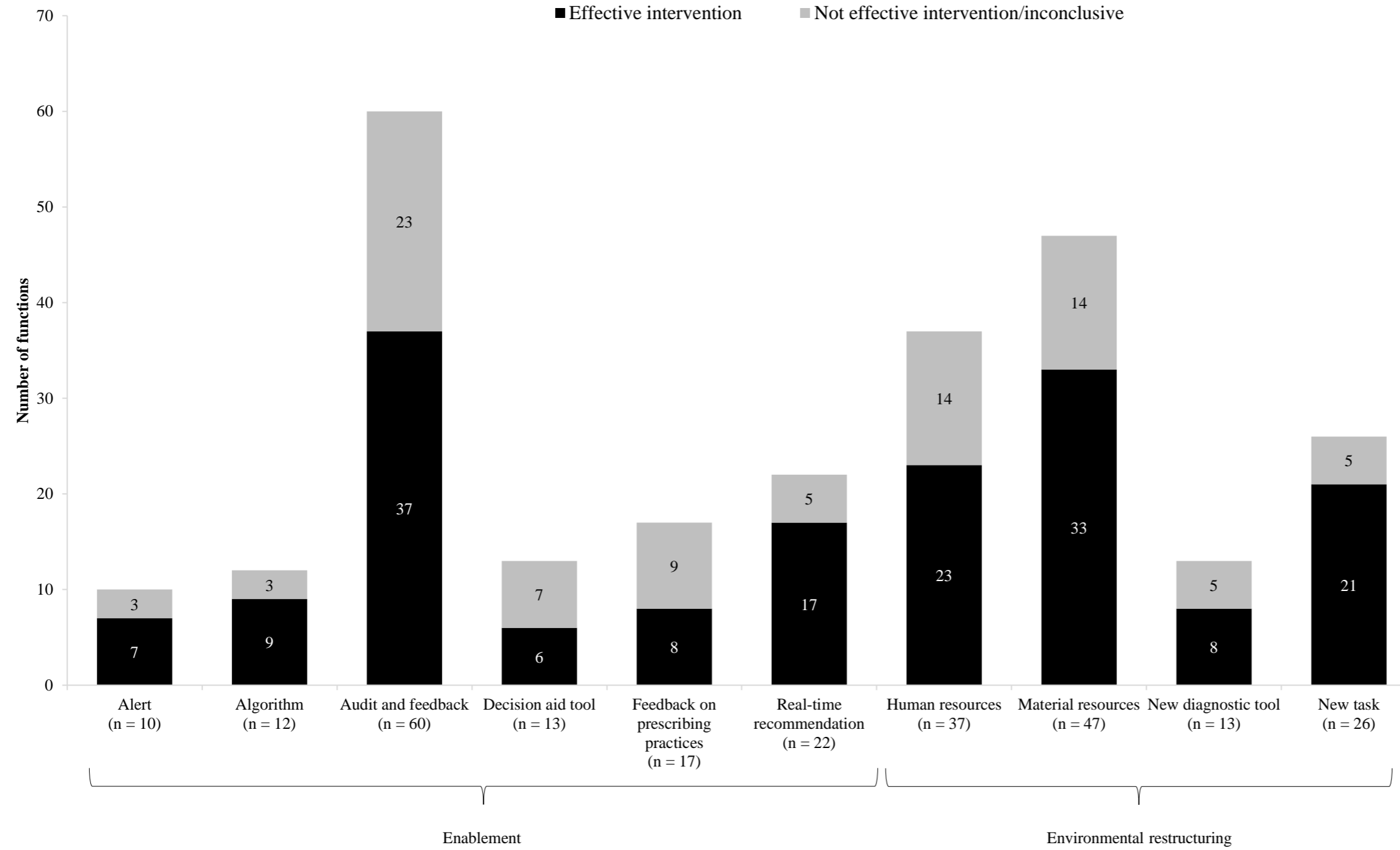


Figure 2a Repartition of interventions effective or not according to intervention functions



	Education (n = 71)	Enablement (n = 107)	Environmental restructuring (n = 90)	Incentivisation (n = 1)	Modelling (n = 5)	Persuasion (n = 21)	Restriction (n = 25)	Training (n = 8)
Effective intervention	46	68	59	1	1	12	18	6
Not effective intervention/inconclusive	25	39	31	0	4	9	7	2
	71	107	90	1	5	21	25	8

Figure 2b Repartition of interventions effective or not according to subcategories of enablement and environmental restructuring functions



	Alert (n = 10)	Algorithm (n = 12)	Audit and feedback (n = 60)	Decision aid tool (n = 13)	Feedback on prescribing practices (n = 17)	Real-time recommenda tion (n = 22)	Human resources (n = 37)	Material resources (n = 47)	New diagnostic tool (n = 13)	New task (n = 26)
Effective intervention	7	9	37	6	8	17	23	33	8	21
Not effective intervention/inconclusive	3	3	23	7	9	5	14	14	5	5
	10	12	60	13	17	22	37	47	13	26