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2   # The quality of studies evaluating antimicrobial stewardship

3   # interventions: a systematic review

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19   **Running title:** Systematic review of antimicrobial stewardship design

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27

28 **ABSTRACT**

29 BACKGROUND:

30 Antimicrobial stewardship aims to optimise antibiotic use and minimise selection of antimicrobial

31 resistance. The methodological quality of published studies in this field is unknown.

32

33 OBJECTIVES:

34 Our objective was to perform a comprehensive systematic review of antimicrobial stewardship research

35 design and identify features which limit validity and translation of research findings into clinical practice.

36

37 DATA SOURCES:

38 The following online database was searched: PubMed.

39

40 STUDY ELIGIBILITY CRITERIA:

41 Studies published between January 1950 and January 2017, evaluating any antimicrobial stewardship

42 intervention in the community or hospital setting, without restriction on study design or outcome.

43

44 METHODS:

45 We extracted data on pre-specified design quality features and factors that may influence design choices

46 including: (1) clinical setting, (2) age group studied, (3) when the study was conducted, (4) geographical

47 region and (5) financial support received.

48

49   RESULTS:

50   The initial search yielded 17,382 articles; 1,008 were selected for full-text screening, of which 825 were

51   included. Most studies (675/825, 82%) were non-experimental and 104 (15%) used interrupted time

52   series analysis, 41 (6%) used external controls and 19 (3%) used both. Studies in the community setting

53   fulfilled a median of 5/10 quality features (IQR 3-7) and 3 (IQR 2-4) in the hospital setting. Community

54   setting studies (25%, 205/825) were significantly more likely to use randomisation (OR 5.9 (95%CI 3.8-

55   9.2)), external controls (OR 5.6 (95%CI 3.6-8.5)) and multiple centres (OR 10.5 (95%CI 7.1-15.7)). From

56   all studies, only 48% (398/825) reported clinical and 23% (190/825) reported microbiological outcomes.

57   Quality did not improve over time.

58

59   CONCLUSIONS:

60   Overall quality of antimicrobial stewardship studies is low and has not improved over time. Most studies

61   do not report clinical and microbiological outcome data. Studies conducted in the community setting were

62   associated with better quality. These limitations should inform the design of future stewardship

63   evaluations so that a robust evidence base can be built to guide clinical practice.

INTRODUCTION

Antimicrobial resistance (AMR) is increasing globally and is a substantial threat to human health[1]. There is a clear relationship between antibiotic exposure and AMR both in populations [2] and individual patients [3]. An estimated 30% of human antibiotic use may be unnecessary and healthcare systems around the world are aiming to achieve substantial reductions in unnecessary antibiotic prescribing. The term 'antimicrobial stewardship' is used to describe use of antibiotics which balances the need for effective individual treatment against the longer-term, societal impact of antibiotic use on antibiotic resistance[4]. Interventions to improve antimicrobial stewardship are usually multifaceted and include periodic or individual patient audit and feedback, decision support, education (educational meetings, educational materials), and antimicrobial formulary restriction[5].

Recognition of the threat posed by AMR and the need to optimise antibiotic prescribing has driven an exponential increase in the publication of studies evaluating antimicrobial stewardship interventions over the last 20 years[6]. Previous systematic reviews have synthesised this evidence with the aim of making recommendations for practice[5,7–12]. These have, appropriately, considered studies with the lowest possible risk of bias but have excluded >50% of published studies in which methodological quality falls below Effective Practice and Organisation of Care (EPOC) criteria[13]. Because the minority of studies are of sufficient quality, many areas of practice rely on a weak evidence base [8]; conducting studies which do not inform practice is a waste of time and valuable resources [5,12].

Journals are beginning to report the minimum standards for antimicrobial stewardship studies to be published [14]; however, there remains a need for consensus on how to design, analyse and report studies evaluating interventions to improve antibiotic prescribing. This would optimise use of valuable resources and strengthen the evidence base in this field. Currently, no overview exists of how antimicrobial stewardship evaluations are designed. We conducted a systematic review of antimicrobial stewardship evaluations with the aim of identifying areas in stewardship evaluation most in need of improvement, to increase validity and translation of research findings into clinical practice.

90 **METHODS**

91 **Search strategy**

92 We searched PubMed for studies evaluating antimicrobial stewardship interventions between January

93 1950 and January 2017. The search strategy (appendix 1) was designed to be as broad as possible.

94 Inclusion criteria were: any study evaluating an antimicrobial stewardship intervention, without restriction

95 on the type of intervention studied and what outcomes were evaluated. Studies were excluded if they

96 were (1) not in English, (2) case-reports, (3) focused mainly on HIV or (4) narrative or systematic reviews.

97 All studies were screened by one author (VAS, CHvW, JI, KH or IvH). In case of duplicate publications,

98 only the original article was included. A random selection of 700 (~4% of total) studies were assessed by

99 a second author (VAS, CHvW, JI, KH or IvH). Uncertainties about the inclusion of studies was resolved by

100 discussion.

101

102 **Data extraction**

103 Studies fulfilling the inclusion criteria were identified by screening on title and abstract. All selected

104 studies then underwent full-text evaluation by one author (VAS, CHvW, JI, KH or IvH) against the

105 inclusion and exclusion criteria and data was subsequently extracted using a standard data extraction

106 template (appendix 2). Data were extracted on study characteristics (i.e. title, authors, year of

107 publication), design quality features, and factors possibly associated with methodological quality. If no

108 funding was reported it was assumed that studies received no financial support. Authors were not

109 contacted in case data were missing or incomplete. A random selection of 10% of the studies were

110 extracted by a second author. We followed the PRISMA criteria for the reporting of systematic reviews

111 (appendix 3) [15].

112

113 **Selection of quality features, and factors associated with quality**

114 In February 2017 we established an international Consensus Working Group funded by the Joint

115 Programming Initiative on Antimicrobial Resistance (JPIAMRWG-010) to develop recommendations on

116 the design, analysis and reporting of antimicrobial stewardship evaluations. The working group

117 coordinators (VAS, CHvW, ML, ASW, MB) invited members to the consensus group based on their

118 expertise on antimicrobial stewardship and/or trial methodology, ensuring that all key clinical areas

119 (primary care, secondary care, intensive care medicine and paediatrics) were represented.   The

120 consensus group agreed that a review to identify areas in stewardship evaluation most in need of

121 improvement to increase validity and translation of research findings into clinical practice was required.

122 For this purpose, existing quality scores were not applicable because these focus solely on

123 methodological quality. The group selected quality features and factors likely to underlie design quality

124 and features based on plenary group discussion during the consensus meeting. Ten quality features were

125 selected for assessment: (1) randomized research design used, (2) external control group assessed, (3)

126 multiple centres used, (4) sustainability of the intervention sufficiently assessed (≥12 months), (5) sample

127 size calculation reported, (6) prospective data collection, (7) correction for confounding factors, (8)

128 primary outcome defined and reported, (9) clinical outcome reported, and (10) microbiological outcome

129 reported.. Selected factors likely to underlie design quality features were (a) the clinical setting

130 (community versus hospital), (b) age group studied (studies including children versus adults, or both), (c)

131 year when study was conducted (newer versus older studies, categorised at approximate quintiles: 1977-

132 2004, 2005-2010, 2011-2013, 2014-2015, 2016-2017) (d) geographical region, and (e) financial support.

133 The quality features and corresponding categorizations are shown in table S1.

134

135 **Statistical analysis**

136 Descriptive statistics were used to describe the quality features of included studies. Differences stratified

137 by subgroup were displayed using spider graphs (Microsoft Excel, version 2010). To assess the

138 independent relationship between factors and quality features we performed multivariable logistic

139 regression models with backward stepwise selection (exit p-value >0.10), presenting odds ratios and 95%

140 confidence intervals in a heat map displaying the strength of the association (Microsoft Excel, version

141   2010). Analyses were performed using the Statistical Package for the Social Sciences for Windows

142   (Version SPSS 21.0.0.0).

143

144   **RESULTS**

145   The initial search yielded 17,382 articles. After title and abstract screening, 1,008 articles were selected

146   for full-text screening (figure 1). Of these, 183 were excluded leaving 825 articles for full assessment

147   (appendix 4). Among 700 randomly selected articles that were screened by a second author, 640/700

148   (91%) were excluded by both authors, 23/700 (3.3%) were selected for inclusion by both authors, 13/700

149   (1.8%) were selected for inclusion by only the first author, and 24/700 (3.4%) were selected for inclusion

150   by only the second author, resulting in a percentage agreement after title/abstract screening of 95%, with

151   a moderate interobserver agreement (Cohen's kappa: 0.53). After discussion of the full text articles,

152   consensus about inclusion was reached in 99.5% (696/700) of the selected articles. From the 3.4%

153   (24/700) studies that were newly identified by a second author, 7/700 (1.0%) were considered correct

154   inclusions after discussion. Therefore, the low proportion of missed papers justified not screening in

155   duplicate. Among the 83 articles selected for double data-extraction by a second author, the percentage

156   agreement per variable ranged from 91%-100%, with all the quality features showing an agreement of

157   ≥95%.

158

159   **Characteristics of included studies**

160   A total of 825 studies were included, In the community setting, most studies were multicentre (72%,

161   148/205) and the commonest study designs were before-after studies without an interrupted time-series

162   (ITS) analysis (23%, 48/205), randomised controlled trials (14%, 28/205), and parallel cluster randomised

163   trials (15%, 30/205)(Table 1). Among the included studies in the hospital setting, most were single centre

164   (84%, 519/620) and the commonest study designs were before-after studies without an ITS analysis

165   (59%, 365/620), before-after studies with an ITS analysis (13%, 82/620), and cohort studies without a

166   control group (12%, 75/620). Among the before-after studies without an ITS analysis, the majority were

167 single centre (86%, 352/411), and retrospective (58%, 239/411). In the 86 (10%) cluster randomised

168 studies a median of 28 clusters were randomised, with 57% (49/86) randomising ≥20 clusters, 28%

169 (24/86) randomising <15 clusters, 21% (18/86) randomising <10 clusters, and 9% (8/86) randomising <5

170 clusters. In the hospital setting, 13% (2/13) randomised ≥20 clusters, while in the community setting 65%

171 (64/71) randomised ≥20 clusters. A minority of studies were conducted in children (12%, 101/825). Both

172 in the community and the hospital setting, most studies did not target a specific disease or syndrome

173 (31%, 63/205, 55% 324/620, respectively) or specific antibiotic class (86%, 177/205, 69% 427/620,

174 respectively). The majority of interventions were bundles (57%, 470/825). Commonest interventions in the

175 community setting included education (73%, 149/205), audit with periodic feedback (29%, 59/205), and

176 clinical decision support 15% (31/205). In the hospital setting, commonest interventions included

177 education 42% (260/620), audit and feedback on an individual patient level (40%, 245/620), restriction

178 (18%, 113/620), and clinical decision support (18%, 112/620). Both in the community and hospital setting,

179 virtually all included studies reported process measure outcomes (99%, 818/825) (Table 2). Both in the

180 community setting and the hospital the most commonly reported process measures included the

181 proportion of patients treated with antibiotics (59%, 121/205, 21%, 131/620), costs/cost-effectiveness

182 (18%, 36/205, 32%, 200/620, respectively), appropriateness (17%, 34/205, 29%, 178/620, respectively),

183 and defined daily doses (17%, 34/205, 25%, 156/620, respectively). In the community setting, commonest

184 reported clinical outcomes were revisits (11%, 22/205), clinical cure (6%,12/205), and infection (5%,

185 10/205), while in the hospital setting these were mortality (32%, 302/620), length of stay (32%, 201/620),

186 and hospital readmissions (12%, 76/620).

187

188 **Quality features**

189 The percentage of studies including each quality feature is shown in Table 3. Studies in the community

190 setting fulfilled a median of 5 quality features (IQR 3-7), while studies in the hospital setting fulfilled 3 (IQR

191 2-4). None fulfilled all 10 quality features. In the community setting 2% (4/205) fulfilled 9, 16% (33/205)

192 fulfilled at least 8, and 35% (72/205) fulfilled at least 7 quality indicators. In the hospital setting 1% (4/620)

193 fulfilled 9, 3% (19/620) fulfilled 8, and 6% (37/620) fulfilled 7 quality indicators. Of note, there were

194   substantial differences between studies which did and did not use randomised designs to the extent to

195   which other quality features were present. Among the 150 randomised studies, all used an external

196   control group, 71% (107/150) included multiple centres, 64% (97/150) reported a sample size calculation

197   and 96% (144/150) collected data prospectively. In contrast, among the non-randomised studies, 12%

198   (78/675) used an external control group, 21% (142/675) included multiple centres, 11% (76/675) reported

199   a sample size calculation and 43% (288/675) collected data prospectively.

200

201   **Factors associated with design quality**

202   Design quality was considerably better in almost all quality aspects of community versus hospital setting

203   studies (Figure S1A), with more use of randomised designs (46% vs. 9%), external controls (63% vs.

204   16%), sample size calculations (38% vs. 15%), prospective data collection (70% vs. 46%), correction for

205   confounding (55% vs. 25%), use of a defined primary outcome (57% vs. 44%), and involvement of

206   multiple centres (72% vs. 16%). However, community setting studies less often reported clinical (30% vs.

207   54%) and microbiological (8% vs. 28%) outcomes. Community setting remained significantly associated

208   with all these factors in multivariable models (Table 4). From the studies that reported financial support,

209   20% (53/264) were industry funded, and 84% (221/264) were publicly funded. Studies with financial

210   support were of higher methodological quality than studies without (Figure S1B), as they more frequently

211   used randomised designs (31% vs. 7%), external controls (34% vs. 8%), sample size calculations (33%

212   vs. 11%), prospective data collection (63% vs 43%), correction for confounding (46% vs. 21%), a defined

213   primary outcome (56% vs. 39%), and involved multiple centres (46% vs. 16%). Financial support

214   remained significantly associated with these factors in multivariable models (Table 4). In addition,

215   financial support increased the frequency of reporting clinical outcomes in multivariable models. There

216   was little change in design quality over time, other than a decrease in the proportion of studies with

217   prospective data collection (77% in 1977-2004, 67% in 2005-2010, 42% in 2011-2013, 40% in 2014-

218   2015, 39% in 2016-2017) and an increase in studies reporting a clinical outcome (39% in 1977-2004,

219   44% in 2005-2010, 44% in 2011-2013, 53% in 2014-2015, 59% in 2016-2017)) (Figure S1D). These

220   outcomes were significantly associated with calendar time in multivariable models (Table 4), and sample

221 size calculations were independently reported more in later studies. The decrease in studies with

222 prospective data collection is most prominent in studies in the hospital setting (Table S2). There were no

223 large differences between studies performed in children versus adults (Figure S1C). Geographical region

224 was independently associated with randomised designs, using an external control, prospective data

225 collection, performing sample size calculations, reporting a primary, clinical or microbiological outcome,

226 and being multicentre (Table 4).

227

228 **DISCUSSION**

229 In previous systematic reviews of antimicrobial stewardship evaluations, many studies have been

230 excluded due to not fulfilling minimal methodological quality criteria. We have undertaken the first

231 comprehensive systematic review focusing on describing quality, rather than excluding studies based on

232 quality, to facilitate formulating recommendations for improvement. In addition, we evaluated quality

233 features required for validity and translation into practice instead of focusing solely on methodological

234 quality. Our systematic review revealed that the design quality of antimicrobial stewardship evaluations is

235 low, with only a minority of studies reporting clinical and microbiological outcome data. Design quality is

236 considerably better in studies performed in the community setting.

237 We find published evaluations provide a striking lack of evidence for the clinical and microbiological

238 impacts of antimicrobial stewardship interventions. The majority of studies focus exclusively on process

239 measures. While it is clearly essential to establish whether an intervention is effective in changing

240 antibiotic use, reporting clinical outcomes is crucial to assess the safety of antimicrobial stewardship

241 interventions [16,17]. The clinical outcomes reported often utilise routinely collected data, which may

242 explain the differences between the community and hospital setting. In particular, in the hospital setting,

243 commonly used clinical outcomes are mortality and length of hospital stay [18,19]. As indicated by the

244 observed time trends, these outcomes are being used with increasing frequency, probably because

245 extraction of relevant data from electronic health records is becoming more feasible. Such routinely

246 available data are not the most sensitive and patient-relevant outcomes. In the hospital setting, markers

247 of early treatment response such as clinical stability may be preferable. In the community setting, repeat

248 consultations, relapse of infection, and hospital admissions may be more relevant; yet data on these

249 outcomes are not routinely collected [20–22].

250 Very few stewardship studies report microbiological outcomes. This is surprising given that reducing

251 antimicrobial resistance is the ultimate goal of antimicrobial stewardship. However, this is consistent with

252 a meta-analysis on the effect of stewardship interventions on infection and colonisation with antibiotic-

253 resistant bacteria and *Clostridium difficile* infections that showed the literature on this topic is sparse and

254 dominated by low quality research [23]. Some authorities have called for stewardship evaluations to

255 routinely include consideration of the impact of stewardship on resistance [24] but studies generally lack

256 power to determine this. Relationships between antimicrobial exposure and resistance may be more

257 efficiently established through specific mechanistic studies rather than within stewardship evaluations.

258 Our analysis demonstrates that factors that would be expected to effect study design do, whiles others do

259 not. The contrast between the community and hospital setting is striking in terms of the greater use of

260 multicentre, randomised controlled designs. One explanation could be that clusters required for cluster

261 randomisation are more readily available in the community setting. In contrast, clinical outcomes and

262 microbiological data are less readily available in the community setting. Retrospective study designs are

263 therefore less feasible in the community setting.

264 Financial support was associated with better design quality. In addition to the costs inherent to conducting

265 multicentre, prospective studies with longer follow-up, the process of securing funding may drives careful

266 consideration of study validity. Less than half of the stewardship studies reviewed reported external

267 funding. However, our finding of an association between external funding and improved design quality

268 underscore the necessity of external funding to support appropriate implementation and robust evaluation

269 of antimicrobial stewardship programmes [25].

270 Our results show that there is no improvement of design quality over time, which is in contrast to previous

271 reports[5,23]. This may be explained by our evaluation and inclusion of all studies without a pre-selection

272 on study design, while previous reviews only included adequate studies with interpretable data[5]. .

273 In keeping with previous reports we find that the majority of antimicrobial stewardship studies used non-
274 randomised research designs, with before-after studies being the most prevalent. This quasi-experimental
275 research design is commonly used for quality improvement projects. However, such studies are at risk
276 from multiple forms of bias [16,24,26] and the Effective Practice and Organisation of Care (EPOC) criteria
277 strongly discourages the inclusion of before-after studies without an ITS analysis in systematic
278 reviews[13]. Incorporation of properly conducted ITS analysis into before-after studies has the potential to
279 robustly control for time-dependent bias [27] but only 20% (104/515) of before-after studies we identified
280 used ITS analysis. Moreover, it has been shown that contemporary ITS analyses are often performed
281 with an insufficient number of data points [11].

282 This systematic review has several strengths. First, our comprehensive search strategy gives a unique
283 overview of the quality of studies evaluating antimicrobials stewardship interventions. Second, we used
284 the PRISMA reporting guide for systematic reviews [15]. Third, the quality indicators and candidate
285 factors were selected in a consensus procedure as part of a Joint Programming Initiative on Antimicrobial
286 Resistance (JPIAMR) funded consensus group, which was selected to both include experts on the field of
287 antimicrobial stewardship and trial methodology. Finally, this is the first comprehensive systematic review
288 to determine the extent to which published antimicrobial stewardship evaluations include quality features
289 required for validity and translation into practice .

290 The limitations of our review were firstly, we only searched PubMed and excluded non-English studies,
291 which makes it possible that antimicrobial stewardship studies indexed elsewhere and non-English
292 studies were missed. However, if we compare the studies identified by our searching strategy with the
293 largest community and hospital stewardship systematic reviews, only 6 studies were missed due to being
294 indexed elsewhere and 11 due to being non-English. Therefore, this is likely to have had a minimal
295 impact on the total results[5,12]. Secondly, the screening, inclusion, and data extraction was performed
296 by only one investigator that could have resulted in studies being missed, wrongly included or
297 misclassification of the extracted data. To estimate the amount of studies that might be missed, a
298 proportion of the studies were screened and data was extracted by a second author. In this second
299 round, we showed that the percentage of agreement was high, with a moderate interobserver agreement.

Assuming that every disagreement in included studies would have inadvertently excluded a study (1% of 700 studies reviewed twice), we may have missed a maximum of 104 inclusions in the other studies not screened twice. In a systematic review with meta-analysis the consequence of missing or wrongly including a single study could have a large impact on the pooled effect estimate. However, as we did not focus on the outcome of individual studies but rather on the design quality of many studies, given the large number of studies included, it is unlikely that the missed studies would have changed the conclusions. And lastly, the quality indicator definition of a primary outcome was only based on what was described in the manuscript. It is possible that a primary outcome was defined retrospectively based on the observed data in a proportion of the studies.

Concerns about the methodological quality of antimicrobial stewardship studies have been raised before, with several publications making recommendations to improve their scientific methods [16,24,26]. However, have found no improvement in methodological quality over time except for more frequent inclusion of sample size calculation and clinical outcomes. Therefore, there is still a need for clear recommendations to improve antimicrobial stewardship design quality. Recommendations for improvement should especially consider: (1) emphasizing the importance of choosing appropriate clinical and microbiological outcomes, (2) focusing on robust methods to evaluate stewardship interventions in the hospital setting. Implementing these recommendations in future antimicrobial stewardship studies will help in the optimal use of resources to determine which stewardship interventions are most effective to change clinical practice. Building on the work from the systematic review we established a working group of expert investigators in this field. This systematic review identifies the limitations in design features that are most important for validity and translation into clinical practice. The results will be used to formulate recommendations in a white paper that will support investigators with key design decisions, support funders assessing proposals for stewardship studies and enhance the quality and impact of research in this crucial area.

SUPPORT STATEMENT

328

335

336   **CONFLICT OF INTEREST**

337   The authors declare no conflict of interest.

338   Figure 1. Flowchart of the studies included in the systematic literature review


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┌─────────────────────────────┐
│ 17382 articles screened based│
│ on title/abstract            │
└─────────────────────────────┘
            │
            │        ┌──────────────────────────────────────────┐
            ├───────▶│ Excluded after title/abstract screening: │
            │        │ 12046                                    │
            │        └──────────────────────────────────────────┘
            ▼
┌─────────────────────────────┐
│ 1008 articles included for   │
│ full-text evaluation         │
└─────────────────────────────┘
            │
            │        ┌──────────────────────────────────────────┐
            │        │ Excluded after full-text evaluation: 183 │
            ├───────▶│   No stewardship intervention (n=121)    │
            │        │   No full-text available (n=50)          │
            │        │   Not English (n=11)                     │
            │        │   Review article (n=1)                   │
            │        └──────────────────────────────────────────┘
            ▼
┌─────────────────────────────┐
│ 825 articles included for    │
│ assessment of methodological │
│ quality                      │
└─────────────────────────────┘
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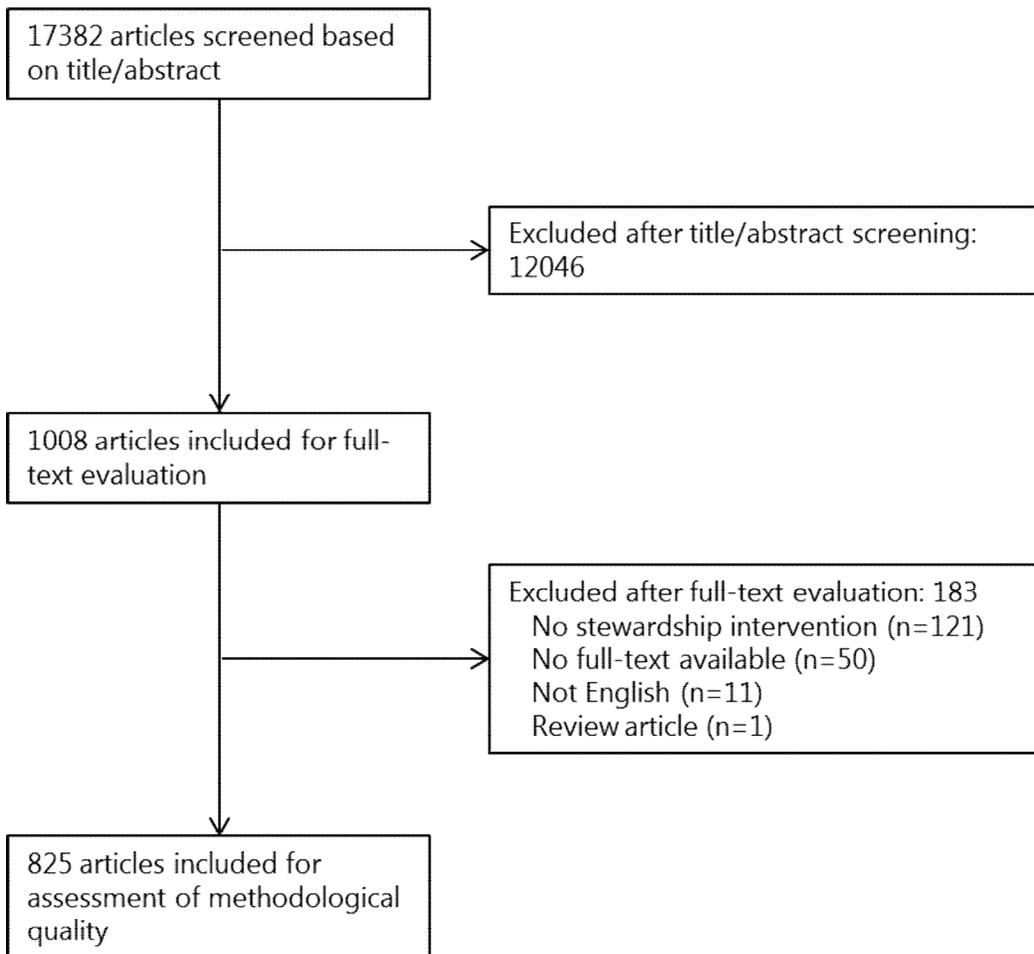
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341

342 Table 1. Characteristics of included studies stratified by studies performed in the community and the
343 hospital setting

Study characteristics	Community (n=205) n (%)	Hospital (n=620) n (%)
Number of patients included (median, IQR)	1255 (278-11230)	423 (186-1398)
Number of centres involved (median, IQR)	27 (8-90)	1 (1-1)
Age		
Adults	64 (31)	285 (46)
Children	33 (16)	68 (11)
Both	108 (53)	267 (43)
Specific disease targeted		
No specific disease targeted	63 (31)	342 (55)
Upper respiratory tract infections	106 (52)	25 (4)
Lower respiratory tract infections	57 (28)	70 (11)
Bacteraemia	0 (0)	42 (7)
Urinary tract infections	18 (9)	27 (4)
Prophylaxis	2 (1)	39 (6)
Sepsis	0 (0)	17 (3)
Skin and soft tissue infections	1 (1)	8 (1)
Abdominal infections	3 (1)	10 (2)
Other	16 (8)	62 (10)
Antibiotic class targeted		
No specific antibiotic class targeted	177 (86)	427 (69)
Cephalosporins	4 (2)	66 (11)
Fluoroquinolones	10 (5)	54 (9)
Carbapenems	0 (0)	48 (8)
Vancomycin	0 (0)	31 (5)
Aminoglycosides	0 (0)	28 (5)
Penicillins	10 (5)	15 (2)
Macrolides	8 (4)	5 (1)
Other	17 (8)	89 (14)
Antimicrobial stewardship interventions		
Education	149 (73)	260 (42)
Audit and feedback – individual patient	12 (6)	245 (40)
Audit and feedback – periodic	59 (29)	82 (13)

Restriction	13 (6)	113 (18)
Clinical decision support	31 (15)	112 (18)
Rapid diagnostic testing	24 (12)	68 (11)
Therapeutic drug monitoring	0 (0)	15 (2)
Guideline implementation	20 (10)	95 (15)
Delayed prescribing	9 (4)	0 (0)
Other	42 (20)	78 (13)
Research designs		
Before-after study	48 (23)	365 (59)
Before-after study (ITS*)	22 (11)	82 (13)
Cohort without control group	6 (3)	75 (12)
Controlled before-after study	22 (11)	19 (3)
Randomised controlled trial (RCT)	28 (14)	40 (6)
Parallel cluster randomised trial	30 (15)	6 (1)
Parallel cluster randomised trial with baseline period	26 (13)	2 (1)
Controlled before-after study (ITS)	7 (3)	12 (2)
Non-randomised parallel cluster study	5 (2)	8 (1)
Factorial cluster randomised trial	7 (3)	0 (0)
Cluster randomised cross-over trial	2 (1)	3 (1)
Stepped wedge cluster randomised trial	0 (0)	1 (1)
Non-randomised cluster cross-over study	0 (0)	3 (1)
Factorial randomised controlled trial (RCT)	1 (1)	2 (1)
Non-randomised stepped wedge study	0 (0)	2 (1)
Adaptive RCT	1 (1)	0 (0)

344   IQR: interquartile range, *ITS: interrupted time series

345 Table 2. Outcomes reported in the included antimicrobial stewardship studies stratified by studies
346 performed in the community and the hospital setting

Process measure outcomes	Community (n=205) n (%)	Hospital (n=620) n (%)
Costs/cost-effectiveness	36 (18)	200 (32)
Appropriateness	34 (17)	178 (29)
Defined daily doses (DDD)	34 (17)	156 (25)
Proportion treated with antibiotics	121 (59)	131 (21)
Recommendation acceptance	6 (3)	114 (18)
Guideline adherence	27 (13)	100 (16)
Duration of treatment	5 (2)	93 (15)
Days on therapy (DOT)	6 (3)	62 (10)
Time to appropriate therapy	3 (1)	71 (11)
Antibiotic knowledge	17 (8)	14 (2)
None	2 (1)	5 (1)
Other	58 (28)	166 (27)
Clinical outcome measures		
None	144 (70)	283 (46)
Mortality	9 (4)	203 (33)
Length of stay	5 (2)	201 (32)
Infection	10 (5)	75 (12)
Hospital readmission	0 (0)	76 (12)
Adverse effects	5 (2)	52 (8)
Revisits	22 (11)	0 (0)
Clinical cure	12 (6)	27 (4)
Intensive care unit admission	0 (0)	24 (4)
Hospital admission	9 (4)	0 (0)
Time to clinical stability	3 (1)	6 (1)
Other	16 (8)	49 (8)
Microbiological outcome measures		
None	188 (92)	447 (72)
Colonization/infection resistant pathogens	17 (8)	146 (24)
Clostridium difficile infections	5 (2)	62 (10)
Other	2 (1)	12 (2)

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348 Table 3. Design quality features of the included studies stratified by studies performed in the community

349 and the hospital setting

Quality feature	Community (n=205) n (%)	Hospital (n=620) n (%)
Randomised research design	95 (46)	55 (9)
External control group	129 (63)	99 (16)
Multicentre	148 (72)	101 (16)
Sample size calculation reported	77 (38)	96 (15)
Prospective data collection	144 (70)	288 (46)
Correction for confounding factors	113 (55)	157 (25)
Primary outcome defined	116 (57)	272 (44)
Clinical outcome reported	61 (30)	337 (54)
Microbiological outcome reported	17 (8)	173 (28)
Sustainability assessed (≥12 months)	115 (56)	347 (56)

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Table 4. Results of stepwise backward selection of multivariable model containing all the factors with the different design quality indicators as outcome. The colours indicate either a strong negative association (OR<1.0) in red, or a strong positive association (OR>1.0) in green. Numbers indicate odds ratio's with 95% confidence intervals

Design quality indicators

Factors		Model 1 Randomised design	Model 2 External control	Model 3 Sample size calculation	Model 4 Prospective data	Model 5 Confounding correction	Model 6 Primary outcome	Model 7 Clinical outcome	Model 8 Microbiological outcome	Model 9 Multicentre	Model 10 Sustainability assessed
Clinical setting	Community (n=205)	5.9 (3.8 - 9.2)	5.6 (3.6 - 8.5)	2.9 (1.9 - 4.5)	1.7 (1.2 - 2.6)	3.0 (2.1 - 4.3)	1.4 (1.0 - 2.0)	0.3 (0.2 - 0.5)	0.2 (0.1 - 0.4)	10.5 (7.1 - 15.7)	
Financial support	Yes (n=385)	4.7 (2.9 - 7.5)	4.1 (2.6 - 6.3)	3.1 (2.1 - 4.7)	2.2 (1.6 - 3.0)	2.5 (1.8 - 3.4)	1.8 (1.4 - 2.5)	1.9 (1.4 - 2.6)		3.0 (2.0 - 4.3)	
Age group studied**	Children (n=101)	1.1 (0.6 - 2.2)	0.8 (0.4 - 1.6)	0.8 (0.5 - 1.4)	1.1 (0.7 - 1.9)		1.0 (0.6 - 1.6)	0.6 (0.4 - 1.0)			1.4 (0.9 - 2.2)
	Both (n=375)	0.6 (0.4 - 1.0)	0.6 (0.4 - 0.9)	0.4 (0.2 - 0.6)	0.5 (0.4 - 0.7)		0.5 (0.4 - 0.7)	0.4 (0.3 - 0.5)			1.6 (1.2 - 2.2)
Year study conducted***	2005-2010 (n=160)	1.0 (0.5 - 1.9)	1.1 (0.6 - 1.9)	2.5 (1.3 - 4.8)	0.4 (0.2 - 0.6)	0.6 (0.4 - 1.0)		0.9 (0.6 - 1.5)	2.1 (1.2 - 3.7)		1.1 (0.7 - 1.8)
	2011-2013 (n=156)	0.5 (0.3 - 1.1)	0.5 (0.2 - 0.9)	1.8 (0.9 - 3.5)	0.2 (0.1 - 0.3)	0.7 (0.4 - 1.2)		1.0 (0.6 - 1.6)	1.7 (1.0 - 3.0)		1.6 (1.0 - 2.5)
	2014-2015 (n=173)	0.4 (0.2 - 0.8)	0.5 (0.2 - 0.9)	2.5 (1.3 - 4.9)	0.1 (0.1 - 0.2)	1.1 (0.7 - 1.8)		1.3 (0.8 - 2.1)	1.2 (0.7 - 2.1)		1.8 (1.1 - 2.8)
	2016-2017 (n=176)	0.8 (0.4 - 1.5)	0.9 (0.5 - 1.7)	2.5 (1.3 - 4.9)	0.1 (0.1 - 0.2)	1.2 (0.7 - 1.9)		1.7 (1.0 - 2.7)	1.4 (0.8 - 2.4)		1.2 (0.8 - 1.8)
Geographical region****	Europe (n=260)	2.5 (1.5 - 4.2)	2.2 (1.4 - 3.5)	1.6 (1.1 - 2.5)	2.8 (1.9 - 4.1)		1.1 (0.8 - 1.5)	1.1 (0.8 - 1.6)	0.9 (0.6 - 1.4)	2.0 (1.3 - 3.1)	
	Asia (n=128)	2.6 (1.3 - 5.0)	2.4 (1.3 - 4.4)	1.1 (0.6 - 2.0)	1.7 (1.1 - 2.7)		0.4 (0.3 - 0.7)	1.8 (1.1 - 2.8)	1.2 (0.8 - 2.0)	1.0 (0.6 - 1.8)	
	Oceania (n=36)	1.6 (0.6 - 4.2)	1.5 (0.6 - 3.7)	0.5 (0.1 - 1.4)	1.8 (0.8 - 3.9)		0.5 (0.2 - 1.0)	0.5 (0.2 - 1.0)	0.2 (0.1 - 0.8)	0.9 (0.4 - 2.2)	
	Africa (n=29)	4.0 (1.1 - 14.5)	3.3 (0.9 - 11.8)	1.8 (0.5 - 5.8)	2.0 (0.6 - 6.2)		0.9 (0.3 - 2.5)	1.8 (0.6 - 5.3)	0.2 (0.1 - 1.7)	7.2 (2.0 - 25.1)	
	South America (n=17)	1.8 (0.4 - 7.4)	2.3 (0.6 - 8.4)	2.0 (0.6 - 6.5)	2.2 (0.8 - 6.4)		1.1 (0.4 - 2.9)	1.1 (0.4 - 3.0)	1.3 (0.4 - 3.8)		

*Reference category: studies performed in the hospital setting (n=620), **Reference category: studies performed in adults (n=349), ***Reference category: studies performed before 2005 (n=160), ****Reference category: studies performed in North America (n=368)

Strong negative association   Weak association   Strong positive association
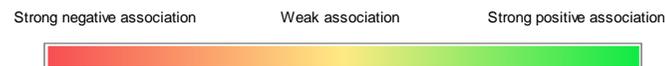
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SUPPLEMENT

Table S1. Definition of the design quality determinants used and corresponding categorisation if applicable

Design quality indicator	Definition	Categorisation (if applicable)
Randomised research design	Allocation of the antimicrobial stewardship intervention or comparator was random. Randomisation is defined as control by means of random allocation at any level (individual or cluster).	Randomised: RCT, c-RCT, cx-RCT, sw-CRT No-randomised: BA(with or without ITS analysis), cBA, cohort studies, non-randomised trials
External control group	The outcome was also assessed in an external control group without antimicrobial stewardship intervention. External indicates that a contemporaneous cluster or group was included in which the intervention under study is not implemented.	Parallel control group: cBA, RCT, non-randomised trials, c-RCT, cx-RCT, sw-CRT No parallel control group: BA, cohort studies
Number of centres	Amount of centres involved in the study, either as control or intervention.	Single centre: 0-1 centre Multicentre: >1 centre
Sustainability of the intervention sufficiently assessed	The duration of follow-up of the cluster after the intervention was introduced to assess the sustainability of the intervention	Yes: Duration of follow-up ≥12 months No: Duration of follow-up <12 months
Sample size calculation reported	A sample size calculation was performed to ensure sufficient power for the primary outcome.	-
Prospective data collection	The data was prospectively collected. If not reported we assumed the data collection to be retrospective.	-
Confounding correction	The intervention effect was corrected for confounding bias, either by randomisation, matching, stratification or correction.	-
Primary outcome	A primary outcome was clearly defined.	-

defined		
Clinical outcome reported	Any clinical outcome was reported. Clinical outcomes include mortality, length of stay, readmissions, revisits, etc.	-
Microbiological outcome reported	Any microbiological outcome was reported. Microbiological outcomes include CDI, colonisation or infection with antimicrobial resistant bacteria	-

RCT: randomised controlled trial, c-RCT: parallel cluster randomised controlled trial, cx-RCT: cluster cross-over randomised controlled trial, sw-CRT: stepped wedge cluster randomised trial, BA: before-after study, cBA: controlled before-after study, ITS: interrupted time-series, CDI: *Clostridium difficile* infection

Table S2. Design quality features changes over time of the included studies stratified by studies performed in the community and the hospital setting

Hospital	1977-2004	2005-2010	2011-2013	2014-2015	2016-2017
Randomised design	10%	17%	6%	6%	8%
External control	12%	20%	6%	8%	11%
Sample size calculation	8%	21%	13%	18%	17%
Multicentre	9%	14%	18%	20%	18%
Prospective data	71%	68%	37%	36%	31%
Confounding correction	24%	22%	19%	29%	30%
Primary outcome	38%	50%	37%	45%	48%
Clinical outcome	43%	51%	50%	58%	66%
Microbiological outcome	21%	38%	32%	23%	27%
Sustainability assessed	53%	50%	55%	65%	54%
Community					
Randomised design	43%	47%	41%	41%	61%
External control	45%	51%	41%	45%	65%
Sample size calculation	19%	44%	35%	48%	52%
Multicentre	68%	75%	78%	69%	71%
Prospective data	89%	65%	57%	59%	74%
Confounding correction	58%	42%	54%	66%	65%
Primary outcome	53%	53%	59%	66%	58%
Clinical outcome	32%	29%	27%	31%	29%
Microbiological outcome	6%	5%	8%	17%	10%
Sustainability assessed	43%	56%	78%	55%	52%

Figure S1. Design quality indicators stratified by factors: (A) community versus hospital setting, (B) financial support versus no financial support, (C) age setting: children, adults or both, (D) old versus new studies, (E) geographical region

A

B

C

Adults (n=349)
Children (n=101)
Both (n=375)

D

1977-2004 (n=160)
2005-2010 (n=160)
2011-2013 (n=156)
2014-2015 (n=173)
2016-2017 (n=176)

E
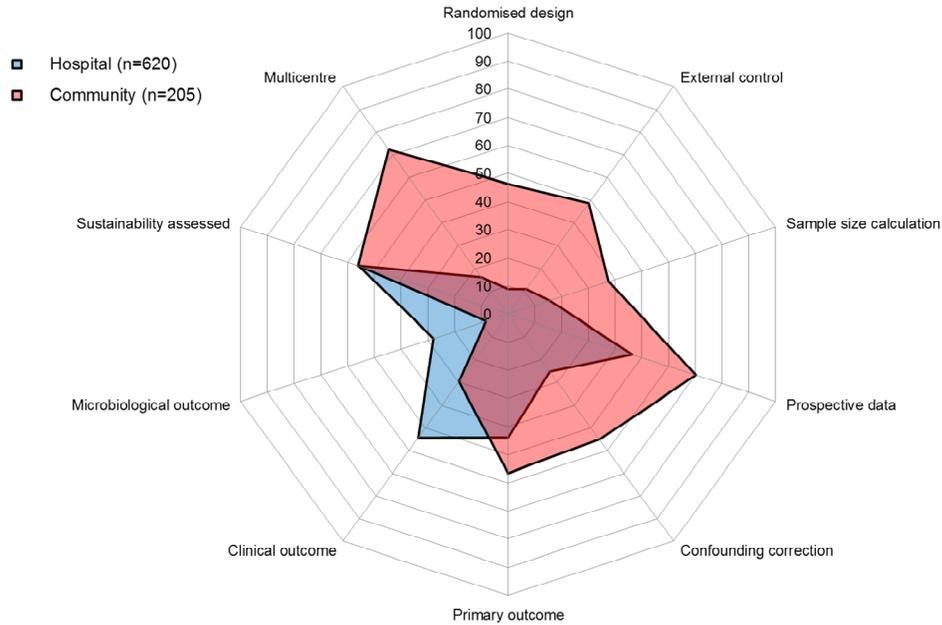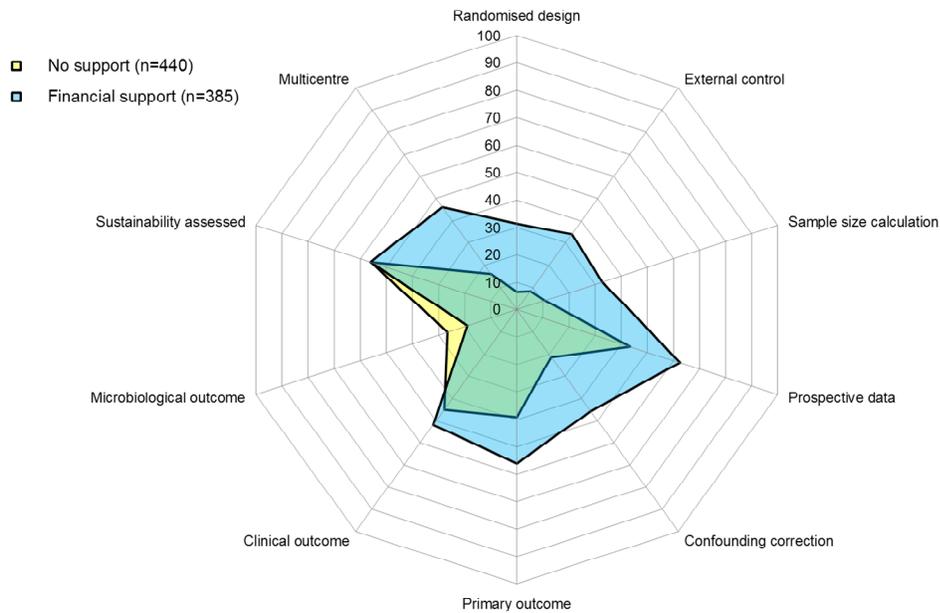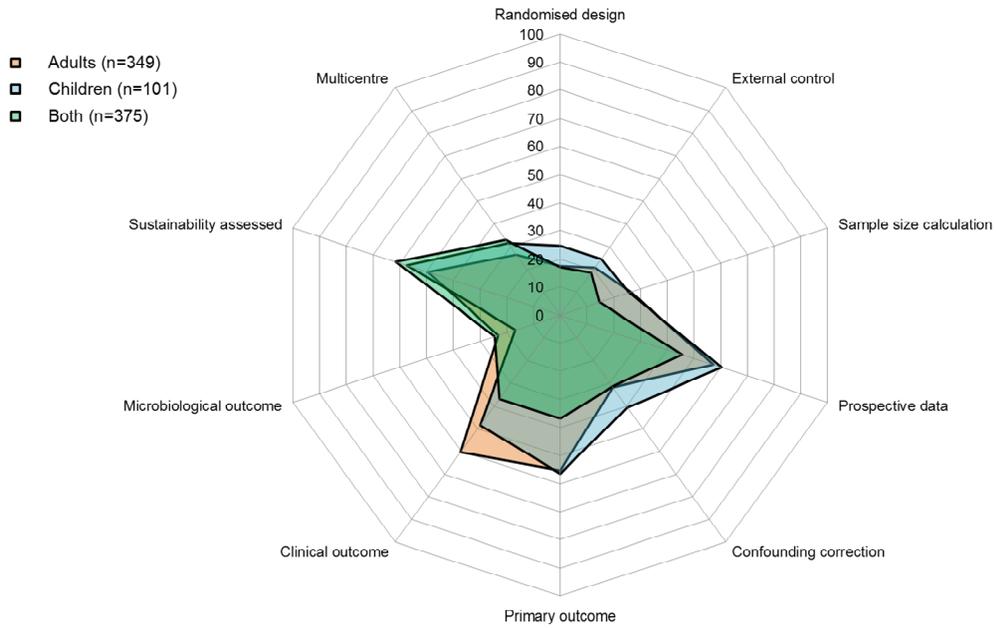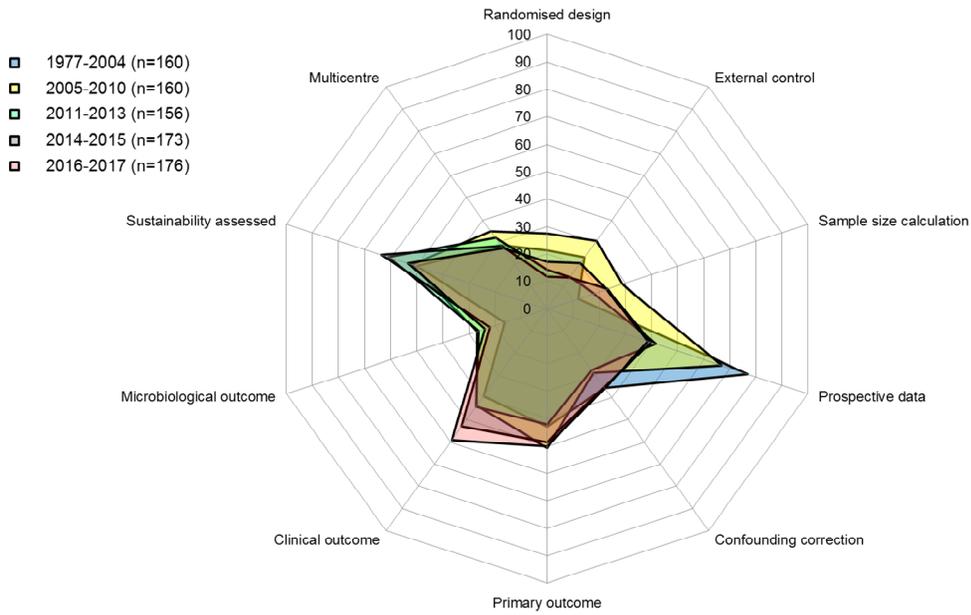
Legend:
- North America (n=368)
- Europe (n=260)
- Asia (n=128)
- Oceania (n=36)
- Africa (n=29)
- South America (n=17)

Axes: Randomised design, External control, Sample size calculation, Prospective data, Confounding correction, Primary outcome, Clinical outcome, Microbiological outcome, Sustainability assessed, Multicentre

Scale: 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100