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Title: The effectiveness of interventions to improve the public's antimicrobial resistance awareness and behaviours associated with prudent use of antimicrobials: a systematic review

Running title: Effectiveness of AMR interventions: systematic review

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1 Synopsis

2 **Background:** A global antimicrobial resistance (AMR) awareness intervention targeting the
3 general public has been prioritised.

4 **Objectives:** To evaluate the effectiveness of interventions which aim to change AMR awareness
5 and subsequent stewardship behaviours amongst the public.

6 **Methods:** Five databases were searched between 2000 and 2016 for interventions to change
7 the public's AMR awareness and/or antimicrobial stewardship behaviours. Study designs
8 meeting the EPOC criteria: non-controlled before and after studies and prospective cohort
9 studies were considered eligible. Participants recruited from healthcare settings and studies
10 measuring stewardship behaviours of healthcare professionals were excluded. Quality of studies
11 was assessed using EPOC risk of bias criteria. Data were extracted and synthesised narratively.

12 **Results:** Twenty studies were included in the review with nine meeting the EPOC criteria. The
13 overall risk of bias was high. Nineteen studies were conducted in high-income countries. Mass
14 media interventions were most common (n = 7), followed by school-based (n = 6) and printed
15 materials interventions (n = 6). Seventeen studies demonstrated a significant effect on changing
16 knowledge, attitudes, or the public's antimicrobial stewardship behaviours. Analysis showed
17 that interventions targeting schoolchildren and parents have a notable potential but for the
18 general public the picture is less clear.

19 **Conclusions:** Our work provides an in-depth examination of the effectiveness of AMR
20 interventions for the public. However, the studies were heterogeneous and the quality of
21 evidence was poor. Well-designed, experimental studies on behavioural outcomes of such
22 interventions are required.

23   **Registration:** PROSPERO International prospective register of systematic reviews (PROSPERO

24   2016:CRD42016050343).

25

Introduction

The rise of antimicrobial resistance (AMR) is a rapidly developing global threat that greatly affects our ability to deliver effective healthcare and results in a financial burden.[1] AMR refers to the ability of a microorganism to adapt and grow despite the presence of antimicrobials. AMR threatens effective treatment of an ever-increasing range of infections.[1] Therefore, increasing AMR is becoming a major public health concern. Although AMR is a naturally occurring phenomenon, inappropriate use of antimicrobials is the main driver of AMR.[1] The demands for the use of antimicrobials are increasing worldwide and because of suboptimal management of these demands, huge quantities of antimicrobials are being misused.[2] Together these highlight the need for effective strategies encouraging prudent use of antimicrobials.

The O'Neil report emphasises the need for AMR awareness interventions directed towards the public and development of a uniform, globally consistent set of AMR messages that could be then tailored to meet the specific demands of local settings.[2] However, the report does not provide recommendations on components of such interventions.[2]

Previous evidence syntheses shows that the overall levels of knowledge and understanding of AMR amongst the public is generally low and members of the public often lack an understanding of their potential contribution to the development of AMR.[3-5] Although high-level evidence demonstrating the effectiveness of interventions in increasing public understanding of AMR exists,[5-7] these evaluations are methodologically diverse. It is therefore challenging to identify what interventions work, why and for whom in order to inform future interventions.

Thus, the aim of this systematic review is to provide the best quality evidence regarding the effectiveness of AMR interventions that change public awareness and their subsequent antimicrobial stewardship behaviours. Although, antimicrobial stewardship is most commonly thought of in medical settings, the word "stewardship" means "taking care of" particularly on behalf of others. Furthermore,

50 a One Health perspective requires the *collaborative* effort of all stakeholders to take the responsibility

51 for the prudent use of antimicrobials. Therefore, within this work, we use the term "antimicrobial

52 stewardship" to explore the public's behaviours related to their prudent use of antimicrobials (such

53 as, but not limited to: adhering to prescribers' directions, not taking or demanding antimicrobial

54 prescription for colds and flu and safe disposal of leftover antimicrobials). We believe an

55 understanding of the public's antimicrobial stewardship is central to engaging them with their part to

56 play in reducing the drivers of AMR on behalf of future generations, other key stakeholders such as

57 prescribers, and the global community.

58 Methods

59 This review was prospectively registered on the PROSPERO International prospective register of

60 systematic   reviews   (PROSPERO   2016:CRD42016050343   Available   from:

61 http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016050343), and is reported in

62 accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

63 statement.[8]

64 *Search strategy*

65 CINAHL, Cochrane Library, EMBASE, MEDLINE and PsycINFO databases were searched for articles

66 published between 2000 and 2016 using keywords associated with the following four concept areas:

67 (1) population - general public; (2) intervention - interventions designed to increase antimicrobial

68 awareness and/or to improve antimicrobial stewardship behaviour amongst the general public; (3)

69 context - AMR or the public's antimicrobial stewardship; outcomes - all relevant short, medium or

70 long-term outcomes related to the public's antimicrobial resistance and/or antimicrobial stewardship

71 behaviours (knowledge/awareness, learning, public behavioural and cognition outcomes). The search

72 strategy incorporated controlled vocabulary thesaurus terms and free text words contained in titles

73 and abstracts. No restrictions were applied to language and publication status. The search strategy

74 was amended according to the functionality of each of the databases. An example of the search

75 strategy applied to MEDLINE is presented in Table S1 (available at JAC Online).

76 In addition to the database search, the reference lists of included papers and previous systematic

77 reviews were searched manually and citation searches were conducted through Web of Science in

78 order to identify additional records.

Study selection

80 Cochrane's Effective Practice and Organization of Care (EPOC) recommendations[9] were used to

81 initially select studies for inclusion in the review. Although, EPOC guidelines suggest the inclusion of

82 Randomised controlled trials (RCT), Non-randomised controlled trials(NRT), controlled before and

83 after studies (CBA), Interrupted time series studies (ITS) and repeated measures studies exclusively,[9]

84 because of the limited number of eligible studies meeting the EPOC criteria, non-controlled before

85 and after studies and prospective cohort studies were also deemed eligible to the review.

86 Interventions targeting the general public population and designed to increase public antimicrobial

87 awareness and/or to improve the public's antimicrobial stewardship were deemed eligible to the

88 review. Furthermore, time bound geographical controls or no exposure comparators and all relevant

89 short, medium or long-term outcomes related to antimicrobial resistance and/or the public's

90 antimicrobial stewardship behaviours were included, while those related to antimicrobial prescribing

91 were excluded as this was regarded as the behaviour of healthcare professionals rather than of the

92 members of the general public. Eligibility criteria applied in this study are presented in detail in Table

93 1.

94 Titles and abstracts of identified records were screened against the eligibility criteria (Table 1) by one

95 of three reviewers (MY, LG, FS) with a 30% sub-set of excluded studies independently checked by

96 another reviewer (MY, LG or FS). The level of agreement on this sub-set was 99%. Disagreements were

97 resolved with the involvement of another, experienced reviewer (LP). Full-texts of papers which

98 appeared to meet the inclusion criteria, or where there was insufficient information within the title

99   and abstract were screened by two out of three independent reviewers (LG, MY, FS), with a fourth

100   reviewer (LP) checking all decisions and resolving any discrepancies. Whenever possible, foreign-

101   language papers were translated by members of the team who have a command in foreign languages

102   (LG, JP), or were translated using Google Translate.

103   ***Data extraction and quality assessment***

104   Two out of three reviewers (LG, MY, FS) independently extracted data from eligible studies using

105   standardised tool, designed for the purpose of the study (Table S2, available at JAC online).

106   For studies that met the EPOC study design criteria (RT, NRT, CBA, ITS),[9] risk of bias was assessed

107   across domains by one reviewer (MY, LG or FS) and checked by a second reviewer (MY, LG or FS) using

108   standard EPOC risk of bias criteria.[9] Disagreements were resolved through consensus or, if necessary

109   consulted with fourth reviewer (LP). Risk of bias assessments were not conducted for non-controlled

110   before and after studies as it was assumed that the risk of bias of these studies was high. No studies

111   were excluded based on quality assessment.

112   ***Data analysis***

113   Given the heterogeneity of the study designs, populations, interventions and outcome measures, it

114   was not possible to pool the results in a meta-analysis. Therefore, we applied an alternative,

115   systematic approach to assessing complex interventions and carried out a narrative synthesis of

116   evidence following the Cochrane Consumers and Communication Review Group's guidelines.[10]

117   Individual study characteristics and findings were summarised and similarities, differences and

118   patterns identified. Studies were grouped to those meeting or not meeting the EPOC criteria and

119   categorised according to the target population. To identify discernible patterns of effectiveness,

120   identified studies were mapped across five categories of intervention effectiveness. These categories

121   were based upon both the strength of the evidence and the position of the primary outcome within

122   the casual chain linking antecedents of behaviour to actual behaviour change. For example, knowledge

123 is understood to be a necessary but insufficient predictor of behaviour as people can develop good

124 awareness and understanding of AMR yet still fail to implement the public's AMR stewardship. The

125 five categories of a relative measure of effectiveness included (1) interventions indicative of clear

126 positive behaviour change in the desired direction, (2) interventions indicative of some positive

127 behaviour change in the desired direction, (3) interventions indicative of positive effect on the

128 antecedent of behaviour, such as knowledge or awareness in the desired direction, (4) interventions

129 indicative of no effect on behaviour or antecedents of behaviour, and (5) interventions indicative of

130 negative effect on behaviour or antecedents of behaviour in a non-desired direction.

131 **Results**

132 Electronic search resulted in the total of 17,312 records. An additional 31 records were identified

133 through reference and citation searching of the included papers. A total number of 60 studies that did

134 not meet eligibility criteria were excluded during the full text reviewing stage. Articles were excluded

135 for not meeting study design criteria, study participants being recruited from healthcare settings,

136 context other than AMR, study outcomes not related to the public's AMR awareness or antimicrobial

137 stewardship, full text record being unavailable, and other reasons such as record being a study

138 protocol, conference abstract of already identified study, short report of already identified study,

139 inability to translate non-English paper, or majority of participants recruited for the study being

140 healthcare workers. A detailed list of excluded papers is presented in Table S3 (available at JAC Online).

141 Following screening, 20 studies that matched the eligibility criteria were included in the review. A

142 detailed process of study selection is presented in Figure 1.

143 *Study characteristics*

144 As shown in Table 2, study designs of the 20 reviewed studies included randomised controlled trials

145 (n = 2),[11, 12] non-randomised controlled trials (n = 3),[13-15] controlled before-after studies (n = 4),[16-19]

146 non-controlled before-after studies (n = 10)[20-29] and a prospective cohort study (n = 1).[30]

147　Apart from one study conducted in Moldova,[16] all studies were conducted in high-income countries,

148　with the majority conducted in the United States (US) (n = 8),[11, 12, 14, 15, 19, 23, 28, 30] or in the United

149　Kingdom (UK) (n = 5).[18, 22, 24, 26, 27] The remaining studies were conducted in Italy,[13] Portugal,[20] Poland,[25]

150　New Zealand,[21] and Australia,[29] while one study was a multisite study conducted in the UK, Czech

151　Republic and France[17] (Table 2).

152　As shown in Table 2, the most common types of interventions were mass media interventions.[13, 14, 18,]

153　[24, 25, 29, 30] Apart from Madle et al. (2008)[24] who used website only, all mass media interventions were

154　multimodal and used a variety of outlets, such as billboards, radio, television, newspapers, magazines,

155　websites, and printed resources such as, posters, brochures, pamphlets, leaflets, stickers or badges

156　distributed to community sites or healthcare settings. Six studies used printed materials interventions,

157　either alone,[12, 15, 21, 23] or in combination with educational presentations,[11, 19] while Stockwell et al.

158　(2010)[28] delivered taught modules to Latino community parents. Other interventions were school

159　based, and included a student peer-taught program,[16] e-bug web game,[22] interactive workshops,[27]

160　school lessons delivered using the "Bug Investigators" pack[26] and presentation followed by

161　discussion,[20] while the intervention delivered in the study by Lecky et al. (2010)[17] involved the delivery

162　of a lesson, printed materials, interactive activities and question & answer session.

163　Comparators were similar across the ten controlled studies.[11-19, 30] With an exception of Lecky et al.

164　(2010)[17] who compared the educational intervention to the usual school curriculum, control groups

165　were not exposed to the interventions.

166　Table 2 shows that the most common outcome measure was change in knowledge, attitudes or

167　beliefs, measured alone (n = 10)[11-13, 15, 17, 20, 22, 24, 26, 27] or in combination with change in the public's

168　antimicrobial stewardship behaviour (n = 8).[16, 18, 19, 21, 23, 25, 28, 29] Two studies measured the public's

169　antimicrobial stewardship behaviour outcomes exclusively (n = 2).[14, 30]

170 ***Quality of studies***

171 Amongst the included studies, nine met the EPOC study design criteria.[9] As shown in Table 3, the

172 overall risk of bias of the included studies was generally high. Apart from one study, [11] all had at least

173 one item assessed as high risk with the number of high risk items ranging from one[15] to five. [18] High

174 risk of bias was most commonly associated with generation of sequence allocation, risk of

175 contamination and other risks.

176 For all studies that met the EPOC criteria, insufficient information was provided for at least 2 of the

177 items which were regarded as unclear risk. None of the studies provided information regarding

178 blinding, and in all studies reporting secondary outcomes, the risk of bias for incomplete secondary

179 outcome data could not be assessed. [13-16] The number of low risk items ranged from one[17, 18] to five [16]

180 with the "selective outcome reporting" item being most commonly assessed as low risk. None of the

181 studies had a low risk score for any of the following items: "allocation concealment", "addressing

182 incomplete secondary outcome data" and "blinding primary outcome data".

183 Risk of bias was not assessed for the non-controlled before-after studies [20-29] and a prospective cohort

184 study. [30] These study designs did not meet the EPOC criteria;[9] therefore, it was assumed that the risk

185 of bias of these studies was high.

186 ***Relative effectiveness of interventions***

187 Reviewed interventions were grouped into five categories of relative measure of effectiveness. As

188 shown in Table 4, six studies demonstrated a clear desired behaviour change following the

189 intervention, while two studies resulted in some desired behaviour change. Desired effect on the

190 antecedent of behaviour was reported in nine papers. One study showed no effect, while two studies

191 demonstrated an increase in drivers of AMR following the intervention.

192 ***Effectiveness of interventions delivered to populations through the lifecycle***

193 In 17 of the studies, the intervention had a significant effect on the outcome of interest amongst the

194 populations through the lifecycle. These included schoolchildren, university students, parents and the

195 general public.

196 *Schoolchildren*

197 All six school-based educational interventions that targeted schoolchildren aged between 9-15 years

198 [16, 17, 20, 22, 26, 27] found a significant increase in knowledge following the educational intervention (Table

199 2). However, Farrell *et al*. (2011)[22] found a significant knowledge change in only 3 out of 21 questions

200 (p ≤0.02), and no overall change in knowledge. The three questions for which significant improvement

201 was reported related to the valuableness of "good microbes", the presence of microbes despite

202 inability to see them, and handwashing being an effective method of removing microbes from the

203 hands. Only one study [16] measured behavioural outcome in addition to beliefs, and found that children

204 in the intervention group were 3.2 times more likely than other students to report that they had not

205 taken an antibiotic for a cold or flu (p <0.001).

206 None of the studies measured long term outcomes of school-based interventions. Post-intervention

207 outcomes were measured immediately following the intervention,[22] or between 1-8 weeks after the

208 intervention. In addition, one study [17] found that the increase in knowledge was maintained at 6 week

209 post intervention in junior but not for senior school students.

University Students

University students were targeted in one experimental study that aimed to investigate whether an

educational intervention (information booklet) resulted in an increase of young adult consumers'

preference for physicians who do not unnecessarily prescribe antibiotics for simple acute upper

respiratory tract infections.[15] This study demonstrated, that exposure to the intervention significantly

increased the mean preferred start date for antibiotics after the onset of an infection from 2.3.-3.9

days (p <0.1) and preference for a physician who would not prescribe antibiotics at day 3 of an

infection (p <0.1). However, this was still well before recommended time of 10-14 days.

Parents

The effect of educational interventions delivered to parents on change in their AMR knowledge,

attitudes or beliefs alone,[11, 12] or in combination with parents' antimicrobial stewardship behaviour

outcomes [16, 19, 23, 28] was measured in six studies. The majority of these interventions were directed to

parents or caregivers of children under the age of 6.[11, 12, 19, 28] In the remaining two studies, intervention

was delivered to households with at least one children over 5 years old[23] and parents of children aged

12-13.[16]

As shown in Table 2, all studies showed a significant increase in knowledge following the interventions.

In addition, four of the reviewed interventions also had a positive effect on changing parents'

antimicrobial stewardship behaviour. Cebotarenco & Bush (2008)[16] found, that parents in the

intervention group were 5.2 times more likely than other parents to indicate they had not taken an

antibiotic for colds or flu (p <0.001). In Trepka *et al.* (2001)[19], the proportion of parents who expected

an antibiotic for their child and did not receive one declined in the intervention area from 14% to 9%,

while it increased from 7% to 10% in the control area (p = 0.003) and the percentage of parents

reporting that they brought their child to another physician because they did not receive an antibiotic

decreased from 5% to 2% in the intervention area and increased from 2% to 4% in the control area (p

= 0.02). Larson *et al.* (2009)[23] found that the percentage of participants reporting using alcohol hand

235 sanitizers has increased from 1.4% to 66.8% following the intervention (p = 0.001) while the

236 percentage of those reporting that at least one member of their household had been vaccinated

237 against influenza has increased from 63.7% to 73.9% (p = 0.001). Stockwell *et al*. (2010)[28] on the other

238 hand, demonstrated that the number of parents reporting that they sought antibiotics without a

239 prescription when their child was sick has decreased from 6 to 1 (p = 0.06).

240 *General public*

241 The general public were the population of interest in eight of the included studies.[13, 14, 18, 21, 24, 25, 29, 30]

242 Apart from Curry *et al*. (2006)[21] who used printed materials in the form of posters and leaflets, all

243 studies were mass media campaigns, including four studies that measured the effects of the national

244 campaign intervention.[18, 21, 25, 29]

245 Five studies demonstrated a significant effect on the general public's knowledge and attitudes [14, 21, 24,

246 25, 29] (Table 2). With respect to antimicrobial stewardship behaviour amongst the public, four studies

247 report a significant effect following the intervention.[14, 21, 25, 29]

248 Gonzales *et al*. (2008)[14] found that visits to paediatricians declined in the intervention group for all

249 conditions but mostly for acute respiratory infections (p = 0.01). Similarly, Curry (2006)[21]

250 demonstrated a significant decrease in the numbers of respondents who reported consulting a doctor

251 for the common cold (p = 0.026). The results of Wutzke, (2006)[29] showed that significantly less

252 participants reported using antibiotics for cough, cold or flu following the intervention (7.4%) in

253 comparison to baseline data (10.8%; percentage point change = 3.4; 95% CI: 1.3–5.5). Mazinska &

254 Hryniewicz, (2010)[25] on the other hand, demonstrated a significant increase in the percentage of

255 respondents who have limited the use of antibiotics (from 27% at baseline to 43% post intervention),

256 have become more disciplined and cautious in their use (from 3% to 24%), and who paid attention to

257 the correct dosage (from 6% to 18%; no p values given).

258   The remaining three studies did not show a significant positive effect on outcomes of interest.[13, 18, 30]

259   In Mainous *et al*. (2009),[30] intervention designed to decrease self-medication with antibiotics

260   surprisingly resulted in significantly greater percentage of the intervention Latino community group

261   using antibiotics without a prescription in comparison with the control group (OR = 1.81; 95% CI, 1.02-

262   3.22). McNulty *et al*. (2010)[18] on the other hand, found no positive effect on participants' knowledge

263   or antimicrobial stewardship behaviour following a national campaign, and there was a significant

264   increase in the percentage of respondents from the intervention area who reported retaining leftover

265   antibiotics (p <0.001). Formoso *et al*. (2013)[13] reported that knowledge consistency with the national

266   campaign messages either worsened (p <0.05) or did not improve in both the intervention and control

267   groups after the intervention.

268   **Discussion**

269   ***Main findings of this study***

270   This systematic review provides an in-depth examination of the effectiveness of interventions that

271   target the public to increase their knowledge, understanding of AMR and engagement with

272   antimicrobial stewardship behaviours. We have also identified patterns between target populations

273   and relative intervention effectiveness. The findings present a complex picture reflecting the

274   heterogeneity of the studies.

275   Our analysis has shown that interventions targeting schoolchildren and parents have notable

276   potential. All interventions that targeted schoolchildren or parents showed a significant effect on the

277   outcome of interest. However, effective school-based interventions tended to only have effects of

278   increasing knowledge. In addition, these studies measured only short-term outcomes. In contrast,

279   interventions targeting parents demonstrated changes in behaviour in addition to knowledge, with

280   the follow up period ranging from 2 weeks [28] to 3 years.[12]

281 With regards to the interventions targeting the general public, the picture is less clear. Although the

282 majority (n = 5) of these studies demonstrated effectiveness of interventions in improving the public's

283 AMR knowledge or their antimicrobial stewardship behaviour, three studied did not, with two

284 showing a decrease in AMR knowledge[13] and in antimicrobial stewardship behaviour.[30] These findings

285 highlight the need to examine differences in the content between these interventions targeting the

286 general public.

287 Patterning of the effectiveness across the type of target population also suggests that different target

288 populations should receive different interventions with different primary outcomes. Nevertheless,

289 targeting children alone is unlikely to make a major contribution to AMR because attitudes and the

290 public's antimicrobial stewardship behaviours may be passed down through generations. Thus, using

291 the power of familial social influence and parental duty where children's AMR education within school

292 is reinforced and boosted by parental interventions in the home, might be a more appropriate

293 approach for the achievement of desired cultural change. This indicates the potential of a multimodal

294 intervention or programmatic approach to AMR related interventions.

295 An ideal approach would be to address the entire population simultaneously, yet segmenting it to

296 target sub-populations. Through such segmentation, or stratification of the general public, diverse

297 tailored interventions addressing different sub-population, would be a strategic way to begin the

298 process of cultural change required to reduce the drivers of AMR.

299 The nature of the increase in knowledge that is needed can also be specified by drawing on other

300 evidence syntheses that has shown that the public's' AMR knowledge and understanding of their

301 contribution to AMR is generally poor.[3] Therefore, in addition to changing the public's understanding

302 of appropriate antimicrobial use, interventions should also target the public's understanding of AMR

303 to enable the public to understand their central role in tackling AMR, and the risks for the intervention

304 recipient, their loved ones and the wider population.

Findings in relation to other research

In their recent paper, Wells & Piddock (2017)[31] argued that amongst other actions, an urgent review of educational campaigns is required in order to fulfil UK and European AMR action plans. Our review addresses this need. Furthermore, to our knowledge this is the first systematic review that provides such an in-depth examination of the effectiveness of AMR related interventions that target the public specifically.

Previous literature focused on the level of the public's AMR knowledge and beliefs,[3, 4] communication interventions or interventions that target both, the public and healthcare professionals.[6] The latter found that multi-component interventions improve the public's knowledge of appropriate antimicrobial use, specifically in relation to antibiotics and that interventions including both, physician and public education appear to be effective in reducing antibiotic use.[6] Similarly, Cross *et al*. (2016)[32] reported that multi-modal communication interventions targeting both the public and clinicians can reduce antibiotic prescribing in high-income countries. Although, our review focused on the general public population specifically, the potential of multi-faceted interventions was also highlighted in our work.

Another previous systematic review by King *et al*. (2015)[7] reviewed the evidence of effectiveness and cost-effectiveness of interventions changing the public' risk related behaviours in relation to antimicrobial use. The review showed that direct contact education interventions were consistently more effective than mass media interventions.[7] This appears to explain our findings on the varying effectiveness of interventions targeting the general public, as majority of these studies used mass media interventions.

There is also a body of evidence on large-scale antibiotic campaigns that although were not eligible for inclusion in our review as the participants were both members of the public and healthcare professions. A literature review showed that there have been numerous multifaceted antibiotic awareness campaigns launched in high-income countries;[33] however, there was substantial

330 heterogeneity in outcomes, including knowledge and awareness, use of antibiotics and antimicrobial

331 resistance, and the interventions themselves often lack a robust grounding in behavioural and social

332 science theory. The majority of campaigns included in the review targeted both the general public and

333 healthcare professionals simultaneously and they appeared to result in a reduction of antibiotic use.[33]

334 It therefore appears that targeting different populations at the same time might result in desired

335 outcomes as healthcare professional's prescribing decisions might also be influenced by the patient,

336 while patient's behaviour might be affected by the prescriber's advice. One such campaign, conducted

337 in the UK in 2014 simultaneously targeted members of the public and healthcare professionals who

338 pledged as Antibiotic Guardians, and showed an increase in AMR knowledge and commitment to

339 pledge behaviour in both surveyed sub-populations.[34] Another antibiotic awareness campaign

340 conducted in Hong Kong, targeted the general public, patients and healthcare professionals in a

341 segmented fashion, and resulted in a significant improvement (p ≤0.002) in respondents' knowledge

342 on prudent use of antibiotics following the campaign.[35] Yet another successful large-scale antibiotic

343 awareness campaign segmented to target the general public and healthcare professionals was

344 conducted in France.[36] The effectiveness of this campaign in reducing the number of antibiotic

345 prescriptions was evaluated and showed a 26.5% (95% CI 33·5–19·6) decrease in the total number of

346 antibiotic prescriptions following the campaign, with the greatest decrease of 35.8% (95% CI-48.3% to

347 -23.2%) in prescriptions issued for children and young adults in the 21-25 years age group (24.1%

348 decrease; CI not provided).[36] These findings further emphasise the potential of programmatic

349 approach to AMR related interventions segmented to different target sub-populations, as suggested

350 previously in our main findings section.

351 ***Strengths and limitations***

352 We have conducted a rigorous search and systematic review accompanied by a narrative synthesis.

353 Although, similar work concerning the effectiveness of interventions aimed to improve antibiotic use

354 has been conducted previously,[32] our work focused on interventions targeting the general public

355   population exclusively and did not include outcomes related to healthcare professionals' AMR

356   awareness or antimicrobial stewardship, such as antibiotic prescribing. Our analysis provides a sense

357   of what is normative within this field, what has been attempted before and what could be repeated.

358   It also provides a unique and valuable contribution to the available literature. However, the study also

359   has limitations.

360   First, because the UK Antimicrobial Resistance Strategy and Action Plan was launched by the

361   Department of Health (DH) in 2000[37], followed by the publication of the WHO Global Strategy for

362   Containment of Antimicrobial Resistance in 2001[1], we limited our search to publications from 2000

363   onwards. This could result in omission of important, older papers. Second, the studies from low- and

364   middle-income countries were underrepresented in our review. Thus, relevance and applicability of

365   our findings to different geographical areas or resource contexts is limited. Third, the risk of bias was

366   assessed only for studies that met the EPOC study design criteria. However, a suitable, validated tool

367   for assessing the risk of bias of non-controlled before and after studies could not be identified.

368   Furthermore, using different instrument could result in ambiguities in relation to the quality of

369   stronger designs. The overall quality of the evidence was rather low. Major problems were associated

370   with randomisation in experimental designs and the evaluation of mass media and other population

371   level interventions. As these kinds of interventions aim for maximum population reach, it is difficult

372   to attain adequate controls or indeed randomise at this population level. Therefore, good quality study

373   designs are systematically less likely to be identified within this kind of population level intervention

374   literature. Notwithstanding this, there was a considerable heterogeneity in outcomes. There are no

375   standardised ways of measuring the public's AMR related knowledge or associated stewardship

376   behaviours. Furthermore, change in knowledge, awareness or beliefs, which were the most common

377   outcome measures across the included studies, might not necessary lead to desired behaviour change.

378   As a result, it is particularly challenging to build cumulative knowledge regarding the effectiveness of

379   interventions to increase the public's engagement with antimicrobial stewardship. Another limitation

380   is that given the problems with the quality of primary research, our measure of relative effectiveness

381   should be treated with caution as this was based on our relative measure and are not equivalent of a

382   strong evidence base within typical evidence based guidance. Finally, we did not conduct an analysis

383   of the cost-effectiveness of reviewed interventions; however, for the majority of studies included in

384   our review, cost effectiveness data was not reported.

385   *Recommendations for future research*

386   Although, our work demonstrated the potential of intervention, that targets particular sub-

387   populations of the general public, taking into account the low quality of reviewed evidence, lack of

388   cost-effectiveness evaluation and underrepresentation of studies from low- and middle-income

389   countries, these findings must be treated with caution. There is a need for well-designed, randomised

390   experimental studies focusing on behavioural outcomes of the interventions. Furthermore, measures

391   of AMR knowledge and stewardship behaviours need to be standardised and there is a need for

392   improvement of the reporting standards to ensure detailed and transparent reporting of intervention

393   components. Finally, considering the underrepresentation of studies from low- and middle-income

394   countries, there is a need for the development and evaluation of similar interventions within such

395   settings.

396   # Conclusions

397   Although some evidence on the effectiveness of interventions that target the general public to engage

398   with the problem of AMR exists, the public's understanding of AMR and their role in combating this

399   problem remains poor. Thus, there is a need for a cultural change and effective engagement of the

400   public in addition to other key stakeholders. This need could be addressed through development of

401   well-designed AMR related interventions robustly grounding within behavioural and social science

402   theory. Our work provided an in-depth examination of the effectiveness of AMR related interventions

403   targeting the members of the public specifically. We suggests that future policy makers should

404   consider multimodal segmented population level intervention that tailors its core messages to

405   children, parents and the wider general public alike, particularly in high-income geographical areas.

406   Future interventions should convey messages that elicit the public's motivation to make their own

407   efforts to address AMR as a growing problem for all and a problem for the present as much as for the

408   future.

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409

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Figures and Tables

Figure 1. Study selection flowchart
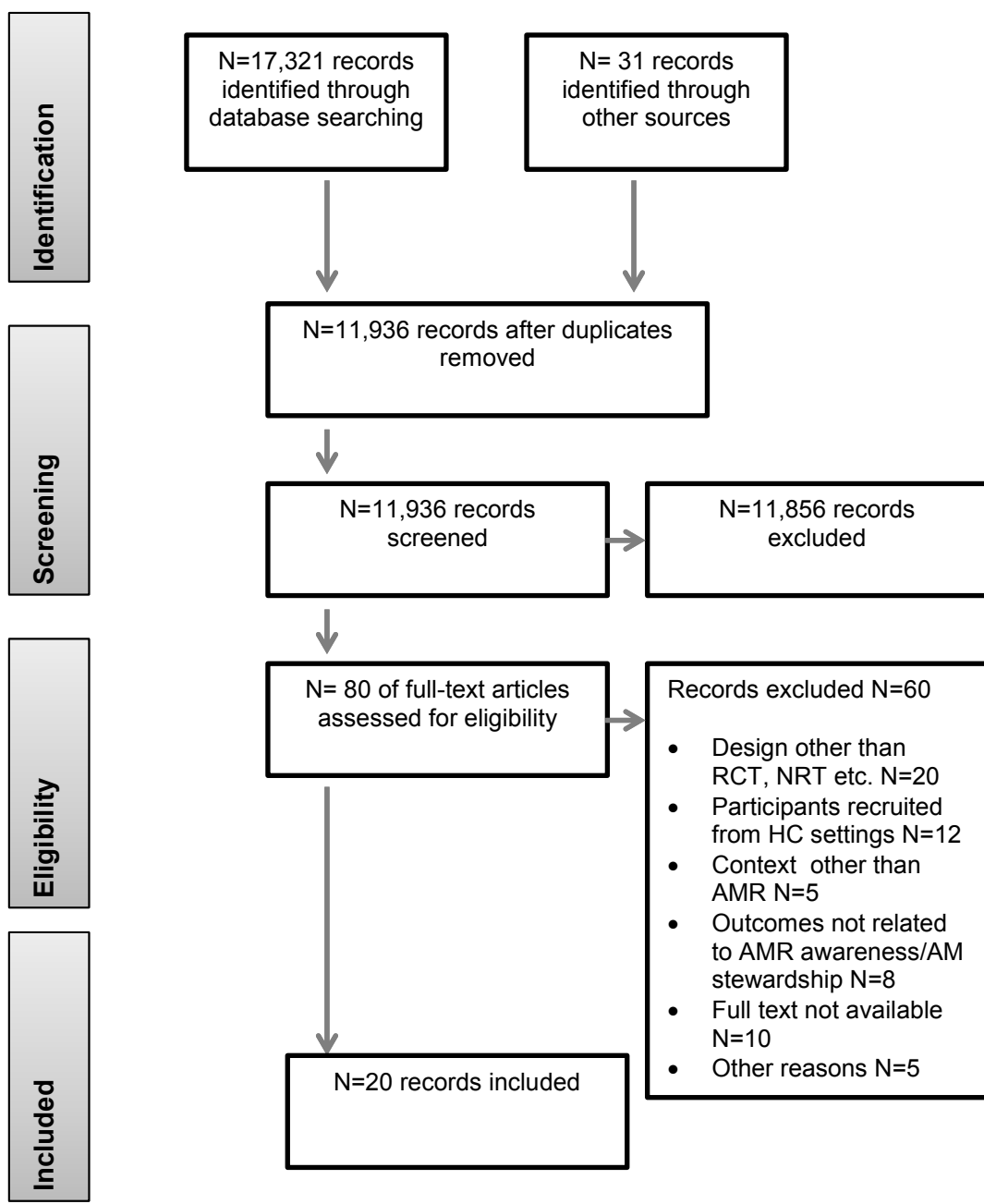
518   Table 1. Review's eligibility criteria

	Inclusion criteria	Exclusion criteria
Design	Randomised controlled trials, non-randomised trial, interrupted time series studies, controlled before and after studies, non-controlled before and after studies and cohort studies.	-
Population	Members of the public	Participants recruited from healthcare settings
Intervention	Intervention designed to increase public antimicrobial awareness and/or to improve antimicrobial stewardship (through mass media, social marketing or printed media campaigns).	-
Comparator	Time bound, geographical controls or no exposure	-
Context	Non-healthcare settings; AMR or the public's antimicrobial stewardship	-
Outcomes	All relevant short, medium or long-term outcomes related to antimicrobial resistance and/or antimicrobial stewardship behaviours (knowledge/awareness, learning, public behavioural and cognition outcomes)	Antimicrobial prescribing
Publication date	Published after January 2000	Published before January 2000

519

520   Table 2. Study characteristics and results of the included studies

Study	Country	Design	Sample	Nature of intervention(s)	Outcome measures	Significant results
Azevedo *et al.* (2013)[20]	Braga, Portugal	NCBA	N = 82 school children	School based presentation followed by discussion.	Knowledge & attitudes	Knowledge of the correct use of antibiotics for bacterial diseases rather than viral diseases rose from 43% to 76% in the post-test (p <0.01). Knowledge of the risk of bacterial resistance to antibiotics from their incorrect use rose from 48% to 74% in the post-test (p <0.05).
Cebotarenco & Bush, (2008)[16]	Chisinau, Moldova	CBA	N = 3586 school children & N = 2716 parents	Educational intervention about the use of antibiotics delivered by student volunteers trained as peer leaders delivered to their classmates & the classmates' parents.	Beliefs & behaviour	Students in both the intervention District & the Post-intervention phase were 3.2 (CI 2.065–4.909) times more likely than other students to indicate they had not taken an antibiotic.
Croft *et al.* (2007)[11]	Wisconsin, USA	RCT	N = 300 parents.	Distribution of printed materials to parents by child care staff; slide presentation delivered to staff.	Knowledge	In parents who were college graduates, the median knowledge scores were 7.0 at intervention centres & 6.5 at control centres (p <0.01).
Curry *et al.* (2006)[21]	Auckland, New Zealand	NCBA	N = 400 general public	National campaign "Wise use of antibiotics". Posters & leaflets delivered to the public attending pharmacies.	Knowledge & attitudes and behaviour	Patients who had ever been to the doctor for a common cold significantly decreased (45% vs 62%; p = 0.0006). They were significantly less likely to feel positive about antibiotics in 2003 for the treatment of a cold (16% versus 33%, p = 0.00001). The perception that antibiotics were beneficial for cold/flu symptoms significantly reduced from 1998 to 2003 (p <0.05); the perceived benefit of antibiotics for tonsillitis increased from 83% to 91% in 2003 (p = 0.014) Significantly less people reported ever attending a doctor for a cold in 2003 Vs 1998 (45% vs 62%; p = 0.0006); & the number of people who would usually see a doctor for a cold decreased from 24% to 15% (p = 0.026).

Farrell *et al.* (2011)[22]	Glasgow, Gloucester and London, UK	NCBA	N = 1736 children	E-Bug web game	Knowledge & attitudes	No overall change in knowledge. Significant knowledge change in 3 out of 21 questions (p ≤0.02).
Formoso *et al.* (2013)[13]	Emilia-Romagna, Italy	NRT	N = 1200 general public	Local mass media campaign (posters, brochures & advertisements on local media) delivered to general population to raise awareness of inappropriate use of antibiotics.	Knowledge	After the intervention, consistency with campaign messages worsened (or did not improve) similarly in both intervention and control areas, the only exception being knowledge on the presumptive antiviral activity of antibiotics, worsening in the intervention area more than control area
Gonzales *et al.* (2008)[14]	Colorado, USA	NRT	N = 1503 general public	Mass media intervention (outdoor & radio advertisements) delivered to general public about use of antibiotics.	Behaviour	Linear regression analysis showed a significant Net differences in monthly paediatric office visit rates between mass media & comparison communities before & after the campaign (p = 0.01).
Huang *et al.* (2007)[12]	Massachusetts, USA	RCT	N = 3142 parents	Community based educational intervention occurred through 3 successive cold & flu seasons. Printed materials: (mailed newsletters, posters, pamphlets, & fact sheets in the waiting rooms of local paediatric providers, pharmacies, & child care centres).	Knowledge & attitudes	The proportion of parents who answered ⊡ 7 of 10 knowledge questions correctly increased significantly in both intervention (from 52% to 64%; p <0 .001) & control (from 54% to 61%; p <0.01) communities. Substantial improvements in percentage correct answers were seen for items on middle ear fluid (41% in 2000; 50% in 2003, p <0.001) & the general question of whether antibiotics were needed for colds & flu (66% in 2000; 77% in 2003, p <0.001)
Larson *et al.* (2009)[23]	Upper Manhattan, USA	NCBA	N = 422 households	Targeted Latino households. Educational materials (colouring book, pamphlets) based on knowledge, attitudes, & practices regarding prevention & treatment of upper respiratory tract infections. Program was delivered during home visits every 2 months.	Knowledge & attitudes and behaviour	After the intervention, the mean composite knowledge scores at baseline 7 end of study were 5.19 (SD = 1.60) & 5.91 (SD = 1.71) (p <0.001), respectively. With regard to reported practices, significantly more participants after the intervention reported using alcohol hand sanitizers (1.4% baseline & 66.8% post-intervention, p = 0.001). Significantly more also reported that one or more members in their household had received the influenza vaccination after the intervention (63.7% at baseline & 73.9% post-intervention, p = 0.001).

Lecky *et al.* (2010)[17]	Gloucestershire and London, England; Nice and Bordeaux, France; Prague and Ostrava, Czech Republic	CBA	N = 2724 school students	School based educational intervention (e-bug) regarding inappropriate antibiotic use delivered to classes of 9-11-year-old (junior) & 12-15 year old (senior) students in state schools Included 45 min lesson hand-outs, worksheets, factsheets, interactive activity 7 a follow-up plenary question &-answer session.	Knowledge	Junior school: Significant change in knowledge, & significant change in retention 6 weeks post-intervention, across countries. Little significant difference in knowledge change between intervention &control, with exception of Czech Republic. Senior school: Significant improvement in knowledge 6 weeks post intervention in Czech Republic. Significant - improvement in knowledge, & knowledge retention between control & intervention in England & Czech Republic
Madle *et al.* (2004)[24]	London, UK	NCBA	N = 177 general public	Open access to the National electronic Library of Infection Antimicrobial Resistance website on the use of antibiotics & antibiotic resistance. The site comprises frequently asked questions &links to evidence based resources.	Knowledge & attitudes	Significant improvements in knowledge about the use of antibiotics & antibiotic resistance in 2 out of 3 statements: (1) "people cannot become resistant to antibiotics" (p <0.001, X2 = 60.357, 95% CI of change: 27.47 to 44.53); (2) "antibiotics do not cure most sore throats" (p <0.001, X2 = 19.22, 95% CI of change: 8.62 to 27.38). Significant changes in the scores assigned by users for 3 out of 4 statements designed to test users' attitudes to the information on the site (p ≤0.003). Expectations that antibiotics should be prescribed were significantly reduced after using the website (p <0.001). Non-HCWs continued to have higher expectations of antibiotics being prescribed than HCW (p = 0.0046 before and p = 0.0098 after using the website).
Mainous III *et al.* (2009)[30]	South Carolina, USA	Prospective cohort study	N = 691 Self-identified Latinos	Mass media educational intervention (pamphlets, radio, newspapers) delivered to local Latino communities about use of antibiotics.	Behaviour	Numbers in the intervention group reporting that they had bought antibiotics without a prescription increased following the intervention compared to baseline (Chi sq test reported as significant but p value not given. The regression analysis showed the strongest predictor of purchase of antibiotics without a prescription in the previous 12 months was past purchase of antibiotics without a prescription outside the United States (OR = 5.72; 95% CI, 3.12-10.48). The regression analysis also showed the strongest predictor of likelihood of importing antibiotics into the United States was past purchase of antibiotics without a prescription outside the United States (OR = 3.01; 95% CI, 1.95-4.65).
Mazinska & Hryniewicz, (2010)[25]	Poland	NCBA	N = 1000 general public	Mass media educational intervention (posters, leaflets, billboards, TV, cinemas, radio, press, magazines, thematic exhibitions, internet) implemented across the country.	Knowledge, attitudes & behaviour	Significant increase in the percentage of people who have limited the use of antibiotics 27-43%, have become more disciplined and cautious in their use from 3-24%, as well as pay attention to the correct dosage 6-18% (no p values given).

McNulty et al. (2001)[27]	Gloucester, UK	NCBA	N = 38 year 5 school children.	School-based intervention to children aged 9-10years at a state school. Included two 90 minute interactive workshops entitled ``Antibiotics and your good bugs''.	Knowledge	Before the workshops 23% & 26% knew antibiotics do not kill viruses but kill good bacteria, compared with 47% & 69% afterwards (p = 0.03 & 0.0001). 45% before & 73% after the workshops correctly answered all the questions (p < 0.0001). Children thought antibiotics helped hay fever, this improved significantly after the workshop (correct answer 28% before, 77% after (p <0.0001). Overall score for 7 questions in the "where are bugs found" section was increased significantly from an average of 80.5% success to 93.2% success (p = 0.0002). The overall score improvement in the "How do bugs spread" section was significant (p = 0.00001).
McNulty et al. (2007)[26]	Gloucestershire, UK	NCBA	N = 198 year 5 and 6 school children	School based intervention. "Bug Investigators" pack about micro-organisms, hygiene & antibiotics The pack included 11 activity sheets, teachers' guide, poster & website.	Knowledge	Children's knowledge improved in all topic areas & was significant in 6 out of the 7 topic areas (p <0.005). Improved knowledge was most significant for what antibiotics do & how to use them (percent improvement 27 (CI 22.8, 31.1) & 31 (CI 23.4, 37.7), respectively; & the value of our own good bugs (16 percent improvement).
McNulty et al. (2010)[18]	England and Scotland, UK	CBA	N = 3718 general public	Mass media campaign about antibiotic use involving posters displayed in magazines & newspapers.	Knowledge & attitudes and behaviour	No positive effect of the campaigns.
Pontes & Pontes, (2005)[15]	Mid-Atlantic region, USA	NRT	N = 105 university students	University based educational intervention (information booklet) to increase young adult consumers' preference for physicians who do not unnecessarily prescribe antibiotics for simple acute upper respiratory tract infections.	Attitudes	Exposure to the intervention significantly increased the mean preferred start date for antibiotics after initiation of an infection from 2.3-3.9 days (p <0.1). Respondents' preferences were significantly greater for the physician who indicated he would not prescribe antibiotics in the intervention (M = 4.84) compared to control (M = 3.91, (p <0.01).
Stockwell et al. (2010)[28]	New York City, USA	NCBA	N = 10 parents	Health literacy intervention regarding upper respiratory tract infection delivered to parents on a "Early Head start" programme. Involved 3x 1.5 hour interactive sessions & provision of kit for care of a child with such an infection.	Knowledge & attitudes and behaviour	The mean composite knowledge/attitude score increased from 4.1 (total possible: 10) to 6.6 (p <0.05). Number of parents reporting that the last time their child was sick they sought antibiotics without a prescription instead of, or in addition to, seeing their health care provider has decreased from 6 to 1 (p = 0.06).

Trepka et al. (2001)[19]	Northern Wisconsin, USA	CBA	N = 365 parents	Nurse educators delivered parent-oriented presentations in community organisations, distributed information pamphlets & displayed posters. Topics covered included antibiotic resistance & use.	Knowledge & attitudes and behaviour	From baseline to post intervention the percentage of parents with high antibiotic resistance awareness significantly increased in the intervention (change: 14.3%: 95% confidence interval [CI]: 6.6, 22.0) but not in the control group (change: 4.3%; 95% CI: -4.1, 12.7; p = 0.015). The proportion of parents who expected an antibiotic for their child & did not receive one, declined in the intervention area (14% to 9%), while it increased in the control area (7% to 10%). The difference between the 2 area changes was -8.4% (95% CI: -13.9,-2.8; p = 0.003). The percentage of parents in the intervention area who brought their child to another physician because they did not receive an antibiotic decreased (5% to 2%), while it increased in the control area (2% to 4%). The difference between the 2 area changes was -4.5% (95% CI: -8.0,-.9; p = 0.02).
Wutzke et al. (2006)[29]	Australia	NCBA	N = 6217 general public	National mass media intervention for consumers delivered during winter months in 2001, 2002, 2003, & 2004. About the inappropriate use of antibiotics for upper respiratory tract infection. Strategies included newsletters & brochures, mass media activity using billboards, television, radio & magazines & small grants to promote local community education.	Knowledge & attitudes and behaviour	There was a significant decline in those who believe taking antibiotics for cold & flu is appropriate, from 28.7% pre-programme in 2002 to 21.7% in 2004 (percentage point change = 7.0; 95% CI: 3.5–10.5). Significant decrease in self-reported use of antibiotics to treat cough, cold or flu, from 10.8% in 1999 down to 7.4% in 2004 (percentage point change = 3.4; 95% CI: 1.3–5.5).

521

522   Table 3. Risk of bias of studies meeting the EPOC criteria.

Study ID	Allocation - sequence generation	Allocation - concealment	Baseline primary outcome	Baseline secondary outcome	Baseline characteristics	Incomplete primary outcome data	Incomplete secondary outcome data	Blinding primary outcome data	Blinding secondary outcome	Contamination	Selective reporting primary outcome	Selective reporting secondary outcome	Other risks of bias
Cebotarenco & Bush	H	H	U	U	L	U	U	U	U	L	L	L	L
Croft et al. (2007)[11]	L	U	U	n/a	U	L	n/a	U	n/a	U	L	n/a	L
Formoso et al. (2013)[13]	H	U	U	U	L	U	U	U	U	U	L	L	H
Gonzales et al. (2008)[14]	H	U	U	L	U	U	U	U	L	H	L	L	H
Huang et al. (2007)[12]	L	U	H	n/a	L	L	n/a	U	n/a	H	H	n/a	H
Lecky et al. (2010)[17]	H	U	U	n/a	U	H	n/a	U	n/a	H	L	n/a	H
McNulty et al. (2010)[18]	H	H	H	n/a	U	U	n/a	U	n/a	H	L	n/a	H
Pontes & Pontes	U	U	U	U	U	U	U	U	U	U	L	L	H
Trepka et al. (2001)[19]	H	U	L	n/a	U	L	n/a	U	n/a	H	L	n/a	H

523

524 Table 4. Patterning of the effectiveness across the type of target population

Study	Interventions indicative of clear positive behaviour change in the desired direction	Interventions indicative of some positive behaviour change in the desired direction	Interventions indicative of positive effect on the antecedent of behavior in the desired direction	Interventions indicative of no effect on behaviour or antecedents of behaviour	Interventions indicative of negative effect on behaviour or antecedents of behaviour in a non-desired direction
Azevedo et al. (2013)[20]			School Children		
Cebotarenco & Bush, (2008)[16]		School Children			
Croft et al. (2007)[11]			Parents; Child Care Facilities		
Curry et al. (2006)[21]	General Public				
Farrell et al. (2011)[22]			School Children		
Formoso et al. (2013)[13]					General Public
Gonzales et al. (2008)[14]	General Public				
Huang et al. (2007)[12]			Parents		
Larson et al. (2009)[23]	Parents				
Lecky et al. (2010)[17]			School Children		
Madle et al. (2004)[24]			General Public		
Mainous et al. (2009)[30]					Latino Community, USA
Mazinska & Hryniewicz, (2010)[25]		General Public			
McNulty et al. (2001)[27]			School Children		
McNulty et al. (2007)[26]			School Children		
McNulty et al. (2010)[18]				General Public	
Pontes et al. (2005)[15]			Young Adults		
Stockwell et al. (2010)[28]	Latino Community Parents, USA				
Trepka et al. (2001)[19]	Parents				
Wutzke et al. (2006)[29]	General Public				

525

Supplementary data

527   1. Supplementary Table S1. An example of search strategy applied for MEDLINE database

528   2. Supplementary Table S2. Data extraction tool designed for the purpose of the study

529   3. Supplementary Table S3. Excluded studies with rationale

530